POST "IBT" ASSESSMENT OF CRITICAL LABORATORY STUDIES ON THE MAMMALIAN AND AVIAN TOXICOLOGY OF FENITROTHION

BY

P.B. CURRY, M.F MITCHELL AND J.R. ROBERTS

NRCC No. 22492

NATIONAL RESEARCH COUNCIL OF CANADA

ASSOCIATE COMMITTEE ON SCIENTIFIC CRITERIA

FOR ENVIRONMENTAL QUALITY

POST "IBT" ASSESSMENT OF CRITICAL LABORATORY STUDIES ON THE MAMMALIAN AND AVIAN TOXICOLOGY OF FENITROTHION

By

P.B. Curry, M.F. Mitchell and J.R. Roberts

Subcommittee on Pesticides and
Industrial Organic Chemicals

Publication No. NRCC 22492

of the

Environmental Secretariat

Crown Copyright Reserved

1984

Available through prepaid orders only from:

Publications, NRCC/CNRC
Ottawa, Canada K1A 0R6

Price: $5.00

The Associate Committee on Scientific Criteria for Environmental Quality was established by the National Research Council of Canada in response to a mandate provided by the Federal Government to develop scientific guidelines for defining the quality of the environment. The concern of the NRCC Associate Committee is strictly with scientific criteria. Pollution standards and objectives are the responsibility of the regulatory authorities and are set for the purpose of pollution control. These may be based on scientific criteria as a starting point but they also take into account the optimal socioeconomic impact of proposed measures as well as the state of existing technology.

The Associate Committee's program includes the evaluation of available information on the probability of effects of contaminants on receptors together with the related fundamental principles and scientific knowledge. In this work particular attention is directed to receptors and contaminants (and their interactions) important to Canada. This Canadian approach is necessary because evaluations made in other countries or regions will not always be applicable to the particular circumstances prevailing in Canada.

Members of the Associate Committee, its Subcommittees and Expert Panels, serve voluntarily and are selected for their individual competence and relevant experience with due consideration for a balance among all sectors in Canada. Responsibility for the quality of study documents rests with the Associate Committee. Each report is carefully reviewed according to a multistage procedure established and monitored by the National Research Council of Canada in order to preserve objectivity in presentation of the scientific knowledge. Publication and distribution of the report are undertaken only after completion of this review process.

Comments on Associate Committee documents are welcome and will be carefully reviewed by the Expert Panels. It is foreseen that these scientific criteria may be revised from time to time, as new knowledge becomes available.

All documents published by the Associate Committee are published in both French and English.

TERMS OF REFERENCE OF THE SUBCOMMITTEE ON PESTICIDES AND INDUSTRIAL ORGANIC CHEMICALS

(1) The preparation of reports critically evaluating and collating the available cause-effect relationships, which permit the estimation of the environmental risks associated with the use of synthetic organic chemicals in Canada - these documents will provide criteria for the evaluation of both present and future use patterns, and

(2) the identification of gaps in available criteria and preparation of recommendations for future research in these areas.

To meet this mandate, the Subcommittee has identified a number of priority compounds for consideration. Comprehensive reports are prepared to bring into perspective the diverse and somewhat obscure observations found in the literature. The documents consist of reviews, summarizing the available criteria and the research required. They also contain as supporting material the available data on which the overview is based.

The mandate of the Subcommittee does not include the setting of objectives and standards, the development of risk assessment, or the establishment of registered uses for pesticides in Canada. Therefore, it does not permit consideration of the engineering, economic, or legal aspects. The Subcommittee is only concerned with scientific information and environmental criteria. The documents do provide one of the components necessary in the consideration and development of risk assessments. Other agencies, both federal and provincial, have the actual responsibility for making decisions about the uses of specific synthetic organic chemicals in Canada, and hence they have the task of bringing about an acceptable balance between the risks and benefits associated with the use of such chemicals by our society.

Inquiries concerning the activities of the Subcommittee should be directed to the Environmental Secretariat of the National Research Council of Canada, Ottawa, Canada.

ACKNOWLEDGEMENTS

We would like to thank Dr. D. Clegg of Health and Welfare Canada for the considerable time and effort offered during the writing of this document. We would also like to thank Earl Maser and Gordon Copp for their editorial assistance and Kathy O'Connor and Mary Legault for typing this document.

TABLE OF CONTENTS

		PAGE
LIST OF TABLES		8
LIST OF APPENDICES		9
ABBREVIATIONS		10
1.0	CRITIQUE AND RECOMMENDATIONS	11
2.0	INTRODUCTION TO THE "IBT" PROBLEM	17
3.0	IBT INVOLVEMENT IN THE MAMMALIAN AND ASSOCIATED AVIAN TOXICOLOGY OF FENITROTHION	19
3.1	Introduction	19
3.2	The Validity of the IBT Studies	19
4.0	TOXICOLOGICAL MANIFESTATIONS OF FENITROTHION	23
4.1	Acute Toxicology	24
4.1.1	Acute Toxicity in Dietary Studies	24
4.1.2	Acute Dermal and Ocular Studies	28
4.1.3	Acute Inhalation Studies	29
4.1.4	Potentiation of Acute Toxicity	32
4.2	Subacute and Chronic Toxicology	32
4.2.1	Subacute Toxicology	33
4.2.1.1	Subacute Toxicity in Dietary Studies	33
4.2.1.2	Subacute Inhalation Studies	33
4.2.2	Chronic Toxicology	35
4.3	Neurotoxicology	37
4.3.1	Delayed Neurotoxicology	39
4.4	Reproduction and Teratogenicity	40
4.5	Mutagenic Activity	42
REFERENCES		101

LIST OF TABLES

TABLE		PAGE
1-1	Excerpts from the most recent NRCC analysis of fenitrothion that identify issues not readdressed in this monograph	12
1-2	The new status of the conclusions and recommendations from the earlier monographs on fenitrothion	13
3-1	Invalid IBT studies on fenitrothion	20
4-1	Acute toxicity of fenitrothion	25
4-2	Summary of acute toxicity of fenitrothion technical and some of its metabolites	26
4-3	Inhalation studies in rats administered four formulations of fenitrothion for 4 hours	30
4-4	Summary of the no-observed-effect levels and the effect levels obtained from subacute studies on fenitrothion	34
4-5	Summary of the no-observed-effect levels and the effect levels obtained from chronic studies on fenitrothion	36
4-6	Summary of the no-observed-effect levels and the effect levels obtained from neurotoxicity studies on fenitrothion	38
4-7	Summary of the no-observed-effect levels and the effect levels obtained from reproduction studies on fenitrothion	41
4-8	Summary of mutagenic studies on fenitrothion	43

LIST OF APPENDICES

APPENDIX		PAGE
I.0	Notice on Subcommittee Monographs Containing Industrial Bio-test Material	44
II.0	Summary of Toxicology Studies on Fenitrothion	45
II.1	Summary of Acute Dietary Studies on Fenitrothion	46
II.2	Summary of Acute Dermal and Ocular Studies on Fenitrothion	52
II.3	Summary of Acute Potentiation Studies on Fenitrothion	57
II.4	Summary of Subacute Dietary Studies on Fenitrothion	58
II.5	Summary of Inhalation Studies on Fenitrothion	62
II.6	Summary of Chronic Dietary Studies on Fenitrothion	69
II.7	Summary of Neurotoxicology Studies on Fenitrothion	73
II.8	Summary of Reproductive and Teratogenic Studies on Fenitrothion	77
II.9	Summary of Mutagenic Studies on Fenitrothion	79
III.0	Trade Memorandum of Guidelines for Pesticide Toxicology Data Requirements	83
IV.0	Validation Summary of Fenitrothion	93

ABBREVIATIONS

AI - active ingredient

BW - body weight

CE - carboxylase (activity)

ChE - cholinesterase (activity)

DLM - dominant lethal mutations

DLT - dominant lethal test

DMSO - dimethyl sulfoxide

EC - emulsifiable concentrate

EEG - electroencephalogram

EMG - electromyogram

GLP - good laboratory practice

HWC - Health and Welfare Canada

IBT - Industrial Bio-test Laboratories

i.p. - intraperitoneal

i.v. - intravenous

i.t. - intratracheal

OP - organophosphorus (pesticide)

NC - p-nitro-m-cresol

NOEL - no-observed-effect level

2-PAM - pralidoxime chloride

PChE - pseudocholinesterase

RBC - red blood cell

S.t. - Salmonella typhimurium

TOCP - tri-o-cresyl phosphate

wk - week

1.0 CRITIQUE AND RECOMMENDATIONS

This report and reports on five other compounds (for details see Appendix I.0), are needed because several toxicology studies included in the NRCC publications were conducted by Industrial Bio-test Laboratories Incorporated (IBT) and, as the U.S. Food and Drug Administration (FDA) subsequently discovered, there were "serious deficiencies in the manner in which studies (at IBT) were being conducted and discrepancies between those studies and their raw data" (EPA 1983). Health and Welfare Canada (HWC) audited the IBT studies on fenitrothion and then identified alternate studies or requested replacements for the studies they considered "invalid". All invalid IBT studies on fenitrothion have now been replaced or alternate studies have been identified.

The objective of this monograph is to reassess, in light of the "IBT" situation, the NRCC assessments of the mammalian and associated avian toxicology of fenitrothion (i.e. NRCC 1975, 1977a, b). Since IBT had conducted studies on avian reproduction, this topic is discussed as well. The reassessment of the other contentious environmental issues discussed in the previous documents is outside the mandate of this monograph but this does not negate their importance. These issues are listed in Table 1-1.

In this reassessment, "valid" IBT studies, replacement or alternate studies, and relevant new data have been considered. While some problems were identified in some of the IBT studies that HWC had considered "valid", similar problems are commonly found in studies carried out during that period and are not unique to the IBT situation. Thus, the term "valid" does not necessarily mean that the studies meet today's protocols, but rather that they provide useful toxicological information and that their limitations are identifiable. The consideration of the new information did not fundamentally change the NRCC criteria previously developed for fenitrothion (see Table 1-2) although some of the questions have been clarified.

Fenitrothion, like most organophosphorus (OP) compounds, is a cholinesterase inhibitor and can cause cholinesterase poisoning in mammals. Cholinesterase inhibition is a key indicator in assessing effects associated with short- and long-term exposure to OPs. In an acute study with fenitrothion, the no-observed-effect level (NOEL) in humans for cholinesterase inhibition was reported to be greater than 0.33 $mg.kg\text{-}BW^{-1}.d^{-1}$. In subacute studies with rats and dogs, the NOELs were reported to be 0.8 and 2.0 $mg.kg\text{-}BW^{-1}.d^{-1}$, respectively. In chronic studies, the reported NOELs for rats and dogs were 0.1-1.0 and <0.9 $mg.kg\text{-}BW^{-1}.d^{-1}$, respectively.

A central issue to be examined in any assessment of an OP compound is its potential to cause delayed neurotoxicity. Although the mechanism for delayed neurotoxicity has not been established, it is not believed to be connected with cholinesterase inhibition. On the basis

Table 1-1. Excerpts from the most recent NRCC analysis of fenitrothion (NRCC 1977a, b) that identify issues not readdressed in this monograph.

Page	
NRCC (1977a) p. 7 (p. 580 in NRCC 1977b)	"Except in a very qualitative sense, we do not have any idea as to which processes (degradation) predominate and thus which toxicants are formed in a given situation. With respect to the emulsifiers and solvents, we have even less information, and particular attention must be given to the dynamics of these compounds."
NRCC (1977a) p. 8 (p. 581 in NRCC 1977b)	"The continued failure of individual researchers to adequately describe the exact nature of their study site makes any extrapolations from residue patterns observed at one site to those expected at another site impossible. A detailed description of the ecosystem before any experimental treatment is undertaken and the exact formulation must be prerequisites for useful enviromental studies."
NRCC (1977a) p. 12 (p. 585 in NRCC 1977b)	"... without more thorough studies any attempts to evaluate the impact of fenitrothion on total fish production will remain unfruitful."
NRCC (1977a) p. 13 (p. 586 in NRCC 1977b)	"... populations of honeybees, solitary wild bees, and bumblebees were sharply reduced following fenitrothion application and (that) recovery took up to 3 years."
NRCC (1977a) p. 13 (p. 586 in NRCC 1977b)	"A return to ... scientific approach to the solution of environmental impact problems with much more effort devoted to designing the key experiments to test the impact of pesticides on the environment."

Table 1-2. The new status of the conclusions and recommendations from the earlier monographs on fenitrothion (NRCC 1975, 1977a, b)[α].

Document	Conclusion	Status of Conclusion	New Conclusion
NRCC (1975)[β] p. 11	"... only limited studies are available on fenitrothion's sublethal effects on birds. It is recommended that relevant classical multigeneration studies of its effects on birds exposed during their breeding cycle must be available before criteria are established"	Unchanged[γ]; the "valid" IBT studies examined were only 1-generation	None
NRCC (1977a) p. 8 (p. 581 in NRCC 1977b)	"... FAO/WHO Joint Meetings on Pesticide Residues have established an acceptable daily intake from food (ADI) of 0.005 mg.kg-BW^{-1} for man..."	Changed because of IBT concerns. FAO/WHO felt that there were gaps in the data which were sufficient to change the ADI	Temporary ADI of 0.001 mg.kg-BW^{-1} set until FAO/WHO meetings in 1984 (FAO/WHO 1982)
NRCC (1977a) p. 9 (p. 582 in NRCC 1977b)	"...with the possible exception of the toxicological assessment of amino fenitrothion, there appear to be data for assessing potential human health effects associated with fenitrothion, its identified contaminants, and its metabolites"	Unchanged; the supporting IBT studies were valid	
NRCC (1977a) p. 9 (p. 582 in NRCC 1977b)	"The absence of adequate inhalation exposure data (on fenitrothion) relevant to spray conditions is noteworthy since inhalation and dermal contact appear to be the major routes of human exposure... studies on animal species utilizing exposure to relevant-sized droplets are essential"	Changed; exposure estimations are now available from a computer model (Crabbe and Reid 1980) and more detailed animal studies have been conducted	Since it is now known that dermal contact is generally the major exposure route (Wolfe et al. 1972), inhalation exposure is not of prime importance for the general population

Table 1-2. (Cont'd)

Document	Conclusion	Status of Conclusion	New Conclusion
NRCC (1977a) p. 10 (p. 583 in NRCC 1977b)	With respect to studies on neurotoxicology, the following observations were made: 1. as the length of exposure increases, experience suggests that effects are observed at lower doses; 2. examination of distal nerve tissue may reveal changes not seen in proximal tissue. "... further studies should be designed and undertaken incorporating the above considerations" (delayed neurotoxicity)	Partially changed; the first point remains valid since recent studies on delayed neurotoxicity use single doses rather than extended exposure -the second consideration has been examined in recent studies and well-documented evidence of degeneration of the distal nerve tissue was not found	On the basis of structure-activity relationships, fenitrothion would not be expected to cause delayed neurotoxic effects. Recent studies found no evidence of delayed neurotoxic effects. Recent studies have raised an additional question concerning the possible parallelism between compounds that cause malathion synergism and delayed neurotoxicity (fenitrothion is reportedly a synergist of malathion toxicity)
NRCC (1977a) p. 10 (p. 583 in NRCC 1977b)	"... almost complete absence of toxicological studies on fenitrothion formulations as applied in the field."	Changed; recent studies have considered emulsifiers in acute dermal and ocular, subacute cholinesterase and neurological studies	Studies with mixtures of fenitrothion and major emulsifiers and solvents have indicated that these adjuvants make little difference to fenitrothion's potential to cause cholinesterase or neurotoxic effects However, the adjuvants tested do appear to make the formulations more severe dermal and ocular irritants

[α] Only the conclusions pertinent to the topics discussed in this document have been examined.

[β] The paucity of information on the mammalian toxicology prevented the panel writing NRCC (1975) from drawing many conclusions on this topic.

[γ] An examination of the general literature on the effects of fenitrothion on birds was not carried out. Only those studies conducted by IBT were reviewed.

of comparisons with the structure-activity relationships of compounds known to cause delayed neurotoxic effects (e.g. TOCP and leptophos), fenitrothion would not be expected to cause delayed neurotoxic effects (Eto 1974). Consistent with this observation is that while fenitrothion is known to cause acute neurotoxic effects (inhibition of cholinesterase activity and the resultant muscarinic effects of the nervous system), there is no well-documented evidence that it causes delayed neurotoxic effects (long-term, usually irreversible damage to the long nerves). However, Eto has noted that most synergists of malathion also show high delayed neurotoxicity and fenitrothion has recently been reported to be a powerful synergist of the toxicity of malathion in mice when administered at sublethal doses (Ramakrishna and Ramachandran 1978). These observations clearly show a need to elucidate the mechanism responsible for delayed and long-term neurotoxicity in OPs and to examine further the possible parallelism with malathion synergism. It must be recognized that these examinations are of importance for all organophosphorus pesticides and not only for fenitrothion.

Another central issue with any pesticide is its impact on reproduction. At the highest doses studied, no teratogenic or reproductive effects have been reported in studies treating rabbits, ducks or quail with fenitrothion (i.e. 1.0 mg.kg-BW^{-1} and 100 and 10 mg.kg-diet^{-1}, respectively). The doses administered to ducks and quail were approximately 1/25th and 1/15th of the respective LD_{50}s reported by Heath et al. (1972). While the recent studies on ducks and quail have shown no effect, they were only one-generation studies and it was recommended in NRCC (1975) that multigeneration studies on birds be conducted in order to assess the effects of field application of fenitrothion. The only effect observed in mammals was a decrease in the number and weight of weanlings in rats dosed with fenitrothion at levels about 1/100th of the LD_{50}.

There is little evidence that fenitrothion is a mutagen. Although there were sporadic reports of effects in the dominant-lethal tests in rats, none of the results was statistically significant. The only definite mutagenic effect reported was chromosome aberrations in the seedlings of the bean plant, Vicia faba.

One of the inadequacies identified in NRCC (1977a, b) was the absence of sufficient data on inhalation exposure relevant to spray conditions. A computer model has now been developed that predicts inhalation exposure (Crabbe and Reid 1980), although models of this type are seldom completely validated by field studies. Some field studies and a complete set of inhalation studies on laboratory animals have also been conducted.

Another problem identified in NRCC (1977a, b) was the lack of toxicological studies on fenitrothion formulations as applied in the field. Some recent studies have considered the adjuvants, and it has been reported that the emulsifier Atlox 3409F and the solvent Dowanol TPM make little difference to cholinesterase inhibition associated with fenitrothion. The addition of the emulsifier Sorpol 355 to fenitrothion

also appears to make no significant difference in studies of neurotoxic effects. However, dermal and eye irritation effects did appear more evident when fenitrothion was applied in conjuction with the emulsifiers Triton X100 and Triton X114 and the solvent Cyclosol 63.

RECOMMENDATION:

During the evaluation of the toxicological information on fenitrothion, it was recognized that although fenitrothion did not appear to cause delayed neurotoxic effects, the mechanism of neurotoxicity in general was ill-defined. Since the data base on fenitrothion is probably as complete as that available on any pesticide, the following recommendation applies for all pesticides:

1. INCREASED PRIORITY SHOULD BE GIVEN TO RESEARCH ON THE MECHANISM OF LONG-TERM NEUROTOXICITY (INCLUDING "DELAYED" NEUROTOXICITY) OF OPs IN GENERAL (NOT ONLY FENITROTHION). THE QUESTION OF MALATHION SYNERGISM AND NEUROTOXICITY SHOULD ALSO BE EXAMINED WITHIN THIS CONTEXT.

2.0 INTRODUCTION TO THE "IBT" PROBLEM

In 1977, Canadian and U.S. authorities recognized that irregularities existed in some toxicology reports supporting the registration of a number of compounds. These reports were based on studies conducted by Industrial Bio-test Laboratories Incorporated of Northbrook, Illinois. When Health and Welfare Canada and the U.S. Environmental Protection Agency reviewed the original situation, it was revealed that safety evaluations for registration of many pesticides used in Canada were supported at least in part by IBT studies. Audits of individual studies indicated serious deficiencies in a significant portion, mainly the long-term and multigeneration studies. These were declared invalid when the findings given in the final report were not supported by the raw data. In these situations, the agencies requested new studies. To date, as a result of the IBT situation, four pesticides (chlorbromuron, cyprazine, phosphamidon and tetradifon) have been withdrawn from the Canadian market and the use of two others (captan and allidochlor) has been restricted.

Since IBT conducted mainly mammalian toxicology studies (with the exception of some avian and fish toxicology), it is these sections of the NRCC documents that requires reexamination. As IBT frequently conducted studies under subcontract for other chemical companies, the original authors were often not clearly identified in the references, making it difficult to ascertain which studies in our documents, and indeed in the data base for a chemical were actually conducted by IBT. Nine NRCC monographs, dealing with endosulfan, fenitrothion, Bacillus thuringiensis, polychlorinated biphenyls, chlorpyrifos and carbofuran contain IBT data. In the spring of 1982, the Associate Committee on Scientific Criteria for Environmental Quality sent a notice to the known recipients of NRCC monographs on pesticides explaining the IBT situation as it applies to the documents and cautioning against the use of any criteria that may have been developed on the basis of IBT material (Appendix I.0). At this point, NRCC took on the task of revising and updating these documents in view of the implications of the suspect studies conducted by IBT.

3.0 IBT INVOLVEMENT IN THE MAMMALIAN AND ASSOCIATED AVIAN TOXICOLOGY OF FENITROTHION

3.1 INTRODUCTION

The mandate given to the authors of this monograph, by the Associate Committee on Scientific Criteria for Environmental Quality, was to reassess the scientific areas in the NRCC documents (NRCC 1975, 1977a, b) in which IBT was involved, rather than to update the entire previous evaluations. For fenitrothion this included the laboratory studies on the mammalian and avian toxicology. To this end, all "identified" IBT studies, the appropriate replacement or alternate studies, and recent critical toxicology studies were reviewed. For completeness we have tabulated all the toxicology data on fenitrothion, including the data from the valid IBT studies reviewed in previous documents (Appendix II.0). Although the other contentious environmental issues examined in NRCC (1975, 1977a, b) are not reevaluated here, they could still be important and a separate assessment would be needed to clarify this situation.

The evaluation of mammalian and associated avian toxicology data in the previous NRCC monographs on fenitrothion (NRCC 1975, 1977a, b) was based on 35 studies, 7 of which were conducted by IBT, mostly under subcontract for Sumitomo Chemical Company. Two additional IBT studies on avian reproduction were appended to NRCC (1975) but not evaluated because of time restraints. Five of these nine studies were deemed invalid by Health and Welfare Canada (HWC) (Table 3-1) and hence replacements were submitted by Sumitomo Chemical Company or similar studies were identified by HWC as alternates.

3.2 THE VALIDITY OF THE IBT STUDIES

Any assessment of the quality of a study may be subject to challenge. While there are no absolute protocols for mammalian toxicology studies, guidelines for data requirements have been published by Agriculture Canada (refer to Appendix III.0). These guidelines are under continual review so that present-day standards are much more exacting than those of 10 years ago. Study design is often more sophisticated and experimental techniques more sensitive. While an old study may not meet all present-day protocols, it can still be useful for identifying effects if properly documented so that its limitations can be defined.

Today, minimum standards for a study exist (Good Laboratory Practises (OECD 1982)) and have been designed to ensure that:

1) the science or design of the study be adequate to detect an effect and to identify the cause of an effect at acceptable defined confidence levels;
2) the records of raw data be properly kept; and
3) the final results be reported in detail.

Table 3-1. Invalid IBT studies on fenitrothion (HWC 1983).

IBT Study number	NRCC Reference	Description	Reason Invalid
8580-09445	NRCC (1975) (p. 81)	Neurotoxicity with Sumithion[a] technical in chickens	No pilot study to establish LD_{50} (the 500 $mg.kg^{-1}$ dose used was probably too low); insufficient data on histopathological methods; age of birds unconfirmed (< 1 year old are relatively insensitive)
J9995	NRCC (1975) (p. 81)	Pilot study - Rabbit teratology	No report available - apparently based on J9996 (IBT 1971j)
C-1667	NRCC (1975) (p. 79) NRCC (1977a) (p. 471)	1-yr chronic oral toxicity of Sumithion technical in beagle dogs	-missing data for controls -appears as if a group of test animals was used as the controls after the 90-d test period -not clear to what extent same test material was used in other studies (i.e. 2-yr and 90-d studies in dogs)
C-9997	Not included in NRCC (1975) or (1977a,b)	90-d subacute oral toxicity of Sumithion technical in beagle dogs	-missing raw data on all animals for some parameters and on controls for more parameters
J9992	Not included in NRCC (1975) or (1977a,b)	Acute oral toxicity of Sumithion technical in mallard ducks	-Animals regurgitated after dosing ∴ LD_{50} not valid
F9999	NRCC (1975) (p. 79)	Subacute oral toxicity of Sumithion technical in human ChE	No raw data available
601-04051	NRCC (1975) (p. 80)	Eye irritation with Sumithion in albino rabbits	-minor discrepancies between raw data and reported results; lack of reporting of some deleterious effects

[a] Trade name for fenitrothion.

The Health and Welfare Canada audit of the IBT studies on fenitrothion found that most were acceptable ("valid") according to the criteria adopted for the audit and validation of IBT studies. The unacceptable studies were usually considered invalid because records were improperly kept. Health and Welfare Canada's reasons for invalidating the seven[α] IBT studies relevant to fenitrothion are listed in Table 3-1. Their validation summary for all IBT studies on fenitrothion is included in Appendix IV.0.

There were many recurring problems in some of the IBT studies on fenitrothion but Health and Welfare Canada did not consider them sufficient reason to declare the studies invalid. Such problems are not unique to IBT studies. They include: 1) not giving the age, origin and strain of the test animal; 2) not naming or confirming the nature and purity of the test material (The literature on pesticides indicates that the presence of contaminants in the test material can be an important consideration in the interpretation of study results (NRCC 1975, Appendix I.0)); 3) not specifying the nature of the vehicle or whether the same vehicle was given to the control group; 4) not being able to determine the exact dose the animal received because of the occurrence of emesis at high doses in non-rodent acute studies. (One study, IBT No. J9992, was invalidated on this basis. It is unknown whether this was a common problem since the occurrence of emesis was not reported in all the studies); and 5) not keeping records correctly and completely. (Raw data were often missing or there were minor discrepancies between the raw data and final results although there were usually sufficient data to support the final results. Some studies were declared invalid when such problems were considered to be severe.)

[α] Two of these studies were not included in the earlier fenitrothion documents (NRCC 1975, 1977a, b).

4.0 TOXICOLOGICAL MANIFESTATIONS OF FENITROTHION

Fenitrothion is an organophosphorus insecticide that is used to control the spruce budworm, which inhabits and feeds on coniferous forests. Its main use in Canada is in New Brunswick where approximately 1.6×10^6 ha are sprayed every year (1979 data in Mitchell and Roberts 1984).

Like most OPs, fenitrothion will cause poisoning at sufficiently high doses through inhibition of the cholinergic nervous system. The primary observed effect of fenitrothion is the depression of cholinesterase levels. Delayed neurotoxicity is an important effect of some OPs, but it has not been reported for fenitrothion and would not be expected on the basis of structure-activity relationships (Eto 1974).

Much of the toxicity of fenitrothion is actually due to its oxygen analogue, fenitrooxon, a metabolite formed in both plants and animals. Other metabolites of fenitrothion are present as contaminants in the technical formulation, most at very low levels. However, S-methyl fenitrothion, which can be formed during storage, can reach levels as high as 6% in some technical products (NRCC 1977a, b) and it appears to be more toxic than fenitrothion.

Historically, one serious problem with the assessment of the effects of fenitrothion or any other pesticide has been that it was usually the technical material and not the applied formulation that was studied. Since emulsifiers, solvents and other adjuvants in the technical material are constantly changing and impurities can differ between batches, identification of the material that organisms are actually exposed to is often difficult. The fenitrothion formulations used in Canada between 1972-1979 were mostly water-based and reportedly included the emulsifier Atlox 3409F and the solvent Aerotex 3470 (Safe et al. 1977; EPS 1978; Mitchell and Roberts 1984). The major formulations used today may contain the emulsifier Atlox 3409F, and/or the solvents Dowanol TPM and 585 Diluent (Chevalier et al. 1982; Hartling 1983).

Recently, some toxicological studies have been conducted with fenitrothion and these adjuvants. The results appear to be consistent with earlier studies using fenitrothion alone. When rats were orally administered fenitrothion technical (in ethanol:propylene glycol) alone and in combination with Atlox 3409F or Dowanol TPM, similar cholinesterase effects were reported for each mixture (Durham et al. 1982; see Appendix II.4). In an inhalation study, rats administered fenitrothion technical with Atlox 3409F, Dowanol TPM and distilled water exhibited dose-dependant inhibition of cholinesterases (Breckenridge et al. 1982; see Appendix II.5). The recovery was rapid and similar to that seen in oral studies when fenitrothion was administered alone (Ecobichon and Zelt 1979; Ecobichon et al. 1980; Trottier et al. 1980). In a delayed neurotoxicity study with hens, Kadota et al. (1975b; see

Appendix II.7) administered fenitrothion with the emulsifier Sorpol 355 and water. The observed results were comparable to those reported in an analogous study in which fenitrothion was administered with the standard vehicle Tween 80 (Sumitomo 1977; see Appendix II.7). Therefore, the adjuvants tested do not appear to significantly affect fenitrothion's potential to cause cholinesterase inhibition or delayed neurotoxic effects.

However, in acute dermal and ocular studies conducted with rabbits, fenitrothion administered in combination with the solvent Cyclosol 63 and/or the emulsifiers Triton X100 or Triton X114 reportedly caused mild irritating effects (Bioresearch[α] 1982b, c, d; see Appendix II.2 and Section 4.1.2). A similar study (Sumitomo 1981), in which rabbits were administered fenitrothion technical (alone) at a higher dose of active ingredient, reported no observations of dermal effects and only very mild short-term ocular effects. Additionally, unpublished preliminary results on the pulmonary toxicity of a formulation of fenitrothion used in Quebec (fenitrothion, Cyclosol and 585 Diluent) indicated potentiation of the effects of 2 $mg.kg^{-1}$ of fenitrothion on pulmonary tissue (Chevalier et al. 1982). It is also possible that solvents and other additives have other autonomous toxic effects, independent of fenitrothion.

4.1 ACUTE TOXICOLOGY

4.1.1 ACUTE TOXICITY IN DIETARY STUDIES

For the purposes of this monograph, an "acute toxicity test" refers to the study of effects produced in a short time (≈14 d) by the test material when administered in a single dose (WHO 1958). The IBT studies mentioned in NRCC (1975) on the acute dietary toxicity of fenitrothion were deemed valid by Health and Welfare Canada (see Table 4-1 for a summary of the acute toxicology in NRCC 1975). More recent studies, including some other valid IBT studies, on the acute toxicity of fenitrothion and its metabolites are summarized in Table 4-2. (For a more detailed review see Appendix II.1.) The conclusions in NRCC (1975) (pp. 77 and 127) do not change.

Most earlier studies were conducted on rats and mice and yielded LD_{50} values (oral administration) that ranged from 283 to 1416 $mg.kg\text{-}BW^{-1}$ (NRCC 1975). From recent studies, birds such as the pheasant and quail are apparently more susceptible to fenitrothion and have much lower LD_{50} values (34.5-140 $mg.kg\text{-}BW^{-1}$).

[α] The studies by Bioresearch were received by the authors after Associate Committee review.

Table 4-1. Acute toxicity of fenitrothion (data from NRCC 1975).

Species	Sex	Strain	Route of Administration	LD_{50} (mg.kg-BW^{-1})	Reference
rat	M	-	oral	740	Gaines (1969)
	F	-	oral	570	Gaines (1969)
	F	SD	oral	386	Sumitomo (1970)
	F	SD	oral	456	Sumitomo (1970)
	M	W	oral	283	Sumitomo (1970)
	F	W	oral	475	Sumitomo (1970)
	M	SD	oral	330	Sumitomo (1972c)
	F	SD	oral	800	Sumitomo (1972c)
	M	SD	dermal	800	Sumitomo (1972c)
	F	SD	dermal	1200	Sumitomo (1972c)
	F	SD	dermal	915	Sumitomo (1970)
	F	SD	subcutaneous	335	Sumitomo (1970)
	M	-	i.p.	135	Dubois and Puchala (1960)
	F	-	i.p.	160	Dubois and Puchala (1960)
	-	-	i.v.	33	Miyamoto et al. (1963)
mouse	M	-	oral	1336	Carshalton (1964)
	F	-	oral	1416	Carshlaton (1964)
	M	dd	oral	1030	Sumitomo (1972c)
	F	dd	oral	1040	Sumitomo (1972c)
	F	TO	i.p.	112	Sumitomo (1970)
	M	-	i.p.	115	Dubois and Puchala (1960)
	F	-	i.p.	110	Dubois and Puchala (1960)
	-	-	i.v.	220	Miyamoto et al. (1963)
guinea pig	M	-	oral	500	Dubois and Puchala (1960)
	-	-	oral	1850	Miyamoto et al. (1963)
	M	-	i.p.	110	Dubois and Puchala (1960)
	-	-	i.v.	112	Miyamoto et al. (1963)
cat	-	-	oral	142	Nishizawa et al. (1961)

Table 4-2. Summary of acute toxicity of fenitrothion technical and some of its metabolites (data not included in NRCC 1975).

Compound	Species	Route	Acute LD_{50}	Min. Lethal Dose	Min. Effect Level	Description of Effect	Reference
			(mg-AI.kg.-BW^{-1})				
fenitrothion technical	mouse	oral	870	-	-	-	Rosival et al. (1976)
	rat	oral	490	-	-	-	
	pheasant	oral	34.5	14.7	14.7	-increased lethality, decreased body weight	IBT (1971h) (J9993)
	hen	oral	500 (384-650)[α]	500	250	-decrease in spontaneous motor activity, motor ataxia and irregular respiration	Kadota et al. (1975b)
	Japanese (m) quail	oral	115 (80-166)[α]	95	67.8	-decrease in spontaneous motor activity and motor ataxia	Kadota and Miyamoto (1975)
	(f)	oral	140 (105-186)[α]	95	67.8	"	
	dogs	oral	-	681[R]	316	-clonic convulsions and ataxia	IBT (1971i) (J9994)
fenitrothion technical (formulated)							
fenitrothion (14%) in Cyclosol 63, Triton X114 and distilled water	rat (m)	oral	476	350	350	-increased lethality	Bioresearch (1982a)
	(f)	oral	406	"	"	-general signs of OP toxicity: lethargy, ataxia, reduced motor activity etc.	
fenitrothion (14%) in Cyclosol 63, Triton X100 and distilled water	rat (m)	oral	385	"	"	"	"
	(f)	oral	441				
fenitrothion (14%) in Triton X114 and distilled water	rat (m)	oral	500	"	"	"	"
	(f)	oral	476				

Table 4-2. (Cont'd)

Compound	Species	Route	Acute LD_{50}	Min. Lethal Dose	Min. Effect Level	Description of Effect	Reference
			(mg-AI.kg.-BW^{-1})				
fenitrothion technical (formulated) (cont'd)							
fenitrothion (14%) in Triton X100 and distilled water	rat (m) (f)	oral oral	756 868	"	"	"	"
fenitrooxon "pure"	mallard ducks	oral	12.5 (8.06-19.38)[α]	10	10	-increased lethality	IBT (1971c) (J102)
	pheasants	oral	10.60 (8.55-13.14)[α]	6.81	6.81	-increased lethality	IBT (1971d) (J103)
	hen	oral	35 (21-57)[α]	25	25	-increased lethality	Kadota et al. (1975b)
	dogs	oral	-	68	10.0	-salivation, diarrhea and ataxia	IBT (1971a) (J100)
fenitrothion s-methyl Tsomer	mouse rat (m)	oral oral	320 315	- -	- -	- -	Rosival et al. (1976)
p-nitro-m-cresol	pheasant	oral	-	4.64×10^3	-	-	IBT (1971f) (J105)

[α] 95% confidence limits.

[β] Minimum emetic dose was 215 mg.kg-BW^{-1}, which would cause a much higher dose to be required to kill the animals.

4.1.2 ACUTE DERMAL AND OCULAR STUDIES

Of the two studies reviewed in NRCC (1975), one was an invalid IBT study (Sumitomo 1972e, IBT No. 601-04051). Its replacement study investigated eye and skin irritation in male albino rabbits (Sumitomo 1981) (see Appendix II.2). When 0.1 mL of Sumithion technical was applied to the eyes of 3 rabbits and the eyes were washed 30 seconds later, no ocular lesions were found. When eye-washing was omitted in 6 other rabbits treated otherwise the same, a slight conjunctival hyperemia was found that disappeared 48 hours after application. To test for skin irritation, 0.5 mL of fenitrothion was applied to the abraded and intact skin of 6 rabbits for 24 hours. No lesions, including erythema or edema, were observed. These observations are similar to those in the invalid study (see NRCC 1975).

In the other dermal study, which was not conducted by IBT, Kohli et al. (1974) reported complete cholinesterase inhibition in whole blood taken 48 hours after treatment. The animals were moribund when the blood was taken and suffered fine to coarse tremors[α] (see Appendix II.2).

Similar eye and skin irritation studies to those reported in Sumitomo (1981) were conducted on male albino rabbits by Bioresearch Laboratories Ltd.[β] (1982c, d; see Appendix II.2). Four formulations of fenitrothion, all consisting of 14% fenitrothion technical, were tested. Two of the formulations contained Cyclosol 63 and either Triton X114 or Triton X100, and the other two contained only either Triton X114 or Triton X100. When 0.1 mL of the formulations (0.014 mL of fenitrothion) was applied to the eyes of the rabbits, the formulations not containing Cyclosol 63 reportedly caused the most severe irritating effects (Bioresearch 1982d). The effects were most noticeable when the formulation with fenitrothion and Triton X100 was applied. When the eyes of some of the animals were washed shortly after application, only very mild, short-lived effects such as the occurrence of pannus were noted. The effects seen in these studies were more severe than those reported in the Sumitomo (1981) study in which unformulated technical fenitrothion was administered, although the dose of fenitrothion (active ingredient) was much less (1/7th). A possible explanation may involve the adjuvants contained in the Bioresearch formulations.

In the skin irritation studies (Bioresearch 1982c; see Appendix II.2), 0.5 mL of the 4 above-mentioned formulations was applied to the abraded and intact skin of albino rabbits. Three of the

---

α Tremors were inaccurately reported as tumors in NRCC (1975).

β The studies by Bioresearch were received by the authors after the Associate Committee review.

formulations were reported to be "nonirritants" to rabbit skin and the formulation with Cyclosol 63 and Triton X100 was "virtually nonirritant". Occurrences of mild erythema and/or edema were found in all groups. This is again a stronger effect than that seen in the Sumitomo (1981) study where the dose of active fenitrothion was 7-fold higher. Acute dermal studies with rabbits (Bioresearch 1982b; see Appendix II.2), in which these 4 formulations were administered dermally at 2000 mg.kg-BW^{-1} (280 mg-AI.kg-BW^{-1}), showed no evidence of mortality, although mild to moderate erythema and/or edema were observed. These effects are consistent with observations that solvents and emulsifiers are often irritants and can also increase dermal absorption (Hayes 1975).

4.1.3 ACUTE INHALATION STUDIES[α]

The inhalation studies that were reviewed in NRCC (1975) are subacute studies and are discussed in Section 4.2.1.2. Recently, several acute studies have been conducted.

Pulmonary toxicity was observed in rats administered fenitrothion in a single-dose intratracheally (Chevalier et al. 1982). Dose-dependant acute pulmonary lesions were observed at doses ranging from 2 to 200 mg.kg-BW^{-1}. All lesions, except those in animals exposed to the highest dose level, had disappeared by 180 d. However, it is not clear how these data can be compared with those involving the standard inhalation route.

A series of acute inhalation studies with four formulations of fenitrothion (containing Cyclosol 63 and/or the emulsifiers Triton X100 or X114) were conducted on rats (Bioresearch 1983) (Table 4-3; Appendix II.5). The LC_{50}s (4-h exposure) ranged from ≈0.83 mg-AI.L^{-1} to >1.69 mg-AI.L^{-1}, with the formulation consisting of fenitrothion and Triton X100 being the most toxic. Pulmonary lesions appeared to be treatment-related for all the formulations and occurred at doses as low as 0.83 mg-AI.L^{-1}. A NOEL of 7 mg.m^{-3} (0.007 mg.L^{-1}) was reported by Sumitomo (1973) (see Section 4.2.1.2) for rats administered a fine mist of technical fenitrothion 2 h a day for 5 weeks. If the LD_{50}s[β] are grossly estimated from the LC_{50}s, the highest LD_{50} in these studies is ≈117 mg-AI.kg.BW^{-1} (4-h). This is approximately 1/2 the LD_{50} of 300 mg.kg-BW^{-1} reported for intratracheal administration (Chevalier et al. 1982), although it should be emphasized that the exposure routes are not directly comparable.

[α] These studies were received by the authors after the Associate Committee review (with the exception of Ecobichon et al. (1977)).

[β] Dosage can be estimated assuming an average respiratory rate of 85/min, a tidal volume of 1.0 mL, the deposition of particles <5.8 μm and a body weight of 200 g (after Breckenridge et al. 1982).

Table 4-3. Inhalation studies in rats administered four formulations of fenitrothion for 4 hours (data from Bioresearch 1983).

Formulation	Nominal chamber concentration (mg-AI.L^{-1})	Analytical chamber concentration (mg-AI.L^{-1})	% of droplets <5.8 µm	Est. Maximum Dose[α] (mg-AI. kg-BW^{-1})	Results: LC_{50} (mg-AI.L^{-1}) (4-h)	Results: Est.[β] LD_{50} (mg-AI. kg-BW^{-1}) (4-h)	Results: BW losses	Results: Lung weights	Results: Treatment-related effect
1. fenitrothion tech. (14%) with Cyclosol 63, Triton X114 and distilled water	17.70 22.06 - 42.79	0.603 0.757 1.473 1.689	86 85 69 68	53 66 104 117	(m) 1.50 (1.22-1.84) (f) >1.689	(m) 106 (f) >117	-slight in 2 low dose groups and marked in 2 high dose groups	-no difference	-vascular and inflammatory changes in the lungs of those animals that died
2. fenitrothion tech. (14%) with Cyclosol 63, Triton X100 and distilled water	11.37 23.49 21.43 41.66	0.042 0.865 0.964 1.445	72 83 71 72	3 73 70 106	(m) 1.15 (0.93-1.43) (f) >1.445	(m) 84 (f) >106	-slight in low dose group and marked at higher doses	-no difference	-atelectasis and neutrophil infiltration of alveolar tissue observed in 35% of high dose group in 5% of control
3. fenitrothion tech. (14%) with Triton X114 and distilled water	20.80 28.79	0.875 0.891	80 89	71 81	(m) ~0.891 (f) >0.891	(m) ~81 (f) >81	-significant in high dose males	-dose-related decrease in males and dose-related increase in females	-focal histiocytosis, bronchopneumonia and necrotizing bronchitis observed in 50% of high dose males
4. fenitrothion tech. (14%) with Triton X100 and distilled water	31.29 27.08	0.830 0.976	94 89	80 89	~0.830[γ]	~80	-marked in both groups (most at lower dose)	-no difference	-bronchopneumonia observed in 35% of the low dose group and total histiocytosis in 20% of the low dose group and 5% of high dose group

[α] Estimations are based on an average respiratory rate of 85/min, 1.0 mL tidal volume, a deposition of the % of droplets <5.8 µm and a body weight of 200 g, given the measured chamber concentration of insecticide (after Breckenridge et al. 1982).

[β] Estimation calculations are as for maximum doses, given the LC_{50}.

[γ] 4 males and 3 females died in low dose group and none at high (this may be because nominal chamber concentration was higher in the low dose group).

A comparison can be made between the LD_{50}s estimated from the Bioresearch (1983) study and the exposure estimated for a human in a field situation (Crabbe et al. 1980). When 210 g-fenitrothion.ha^{-1} was applied in New Brunswick by a TBM (Grumman Avenger) aircraft with 11010 TEEJET nozzles, estimates of the average subcanopy aerial concentration of fenitrothion for the first hour were ~6.67 ng.L^{-1} (Crabbe et al. 1980). It can be estimated that, during this period, a human standing at the spray line and breathing 20 litres of air per minute (light activity; ICRP 1975) would inhale 800 ng of fenitrothion, a dosage of 1.33×10^{-5} mg.kg-BW^{-1} for a 60-kg individual. This is six orders of magnitude less than the LD_{50} (66 mg.kg-BW^{-1} for 1-h[α]) calculated for female rats inhaling a formulation of fenitrothion, Cyclosol 63 and Triton X114 (Bioresearch 1983). Note that the LD_{50}s estimated from the Bioresearch (1983) study are only gross estimates based on many assumptions.

A theoretical upper limit vapor exposure can also be estimated for fenitrothion from its vapor pressure (p) and the gas law:

$$pV = nRT$$

where: $p = 7.1 \times 10^{-8}$ atm
V = volume occupied (cm^3)
n = number of moles of fenitrothion in V
R = gas constant = 82.06 $cm^3.atm.deg^{-1}.mol^{-1}$
T = temperature in °K

The concentration at 10°C can be estimated as:

$$\frac{n}{V} = \frac{p}{RT}$$

$$= \frac{7.1 \times 10^{-8}}{(82.06 \times 283)} \text{ mol.cm}^{-3}$$

$$= 3 \times 10^{-12} \text{ mol.cm}^{-3}$$

$$= 8 \times 10^{-4} \text{ mg.L}^{-1}$$

The particle size spectrum is not known for this situation but if we assume 100% inspiration and a respiration rate of 20 L.min^{-1} (ICRP 1975), the vapor exposure for a 60-kg man could be:

$$\frac{20 \times 8 \times 10^{-4} \times 60}{60} = 1.6 \times 10^{-2} \text{ mg.kg-BW}^{-1}.\text{h}^{-1}$$

This exposure would pertain to fenitrothion applied at a rate sufficient to achieve vapor saturation. Saturation is more likely in situations where spills occur in contained areas.

[α] Estimated from the 4-h LC_{50}s reported in Bioresearch (1983).

In a recent report, Ecobichon et al. (1977) describe the reaction of a person accidently exposed, both dermally and through inhalation, to an unknown amount of fenitrothion (see Appendix II.2). She exhibited nonspecific toxic poisoning symptoms (e.g. nausea, blurred vision, diarrhea, abdominal cramps, muscular weakness, mental confusion and tremors) as well as depressed cholinesterase levels and muscular effects that lasted several months.

4.1.4 POTENTIATION OF ACUTE TOXICITY

There were no IBT studies designed to assess potentiation between fenitrothion and other pesticides or impurities in fenitrothion. The literature reviewed by NRCC (1975) showed no evidence of potentiating effects between fenitrothion and several organophosphorus compounds including malathion, but there was evidence of potentiation between fenitrothion and phosphamidon at low doses of fenitrothion (see Appendix II.3). More recently however, Ramakrishna and Ramachandran (1978) studied the potentiation of malathion by fenitrothion by administering the two chemicals sequentially to mice. They found that fenitrothion is a powerful synergist at sublethal doses. For example, when malathion was administered after one-quarter of the LD_{50} of fenitrothion (25 mg.kg-BW^{-1}.d^{-1}), the LD_{50} of malathion decreased fourfold (from 1223 to 355 mg.kg-BW^{-1}.d^{-1}) and hence the toxicity increased. The authors proposed that this phenomenon had not been observed earlier because the two chemicals were usually administered simultaneously.

Fenitrothion's potential for dermal sensitization to itself was tested using albino guinea pigs (Bioresearch 1982e). Four studies were conducted with four individual formulations containing Cyclosol 63 and/or Triton X100 or Triton X114. An initial dose of 0.05 mL of the respective formulations (0.007 mL-AI) was administered intradermally and thereafter the animals received nine 0.1 mL injections of the same formulation over the next 4 weeks. A challenging injection of the same formulation was administered 2 weeks later. While the two formulations containing Cyclosol 63 and Triton X100 or Triton X114 were judged to be moderate dermal irritants, and the other two formulations were mild dermal irritants, no evidence of a sensitizing effect was found with any of the formulations.

4.2 SUBACUTE AND CHRONIC TOXICOLOGY

There are several definitions of subacute and chronic toxicity tests but for this monograph we will utilize those of the WHO (1958). A "subacute toxicity test" is defined as a study of the effects produced by the material when administered in repeated doses over a period up to 10% of the expected life span of the animal. A "chronic toxicity test" refers to the study of the effects produced by the test material when administered in repeated doses over a longer period of time, usually the

major portion of the expected life span of short-lived species, sometimes covering the entire life span and more than one generation of such species.

4.2.1 SUBACUTE TOXICOLOGY

4.2.1.1 Subacute Toxicity in Dietary Studies

IBT conducted only one subacute dietary study, a 2-3 month study performed on man (IBT 1972, IBT No. F9999), which was considered invalid. Alternates to this study have been submitted; one is actually an acute study reported in NRCC (1975). In that study (Nosal and Hladka 1968), fenitrothion was given to 24 subjects in single oral doses (0.042-0.33 mg.kg-BW^{-1}) and the amount of the metabolite, p-nitro-m-cresol (NC), in the urine was determined. The study showed that the quantity of NC eliminated was in direct proportion to the size of the dose. It also showed that all cholinesterase levels were within normal ranges. While p-nitrol-m-cresol is a more sensitive proof of exposure than is cholinesterase determination, it gives no information about the eventual harm to humans. Nosal and Hladka (1968) provide a no-observed-effect level (NOEL) of greater than 0.33 mg.kg-BW^{-1} for cholinesterase inhibition, which due to the different types of studies, cannot be compared to the NOEL (0.1 mg.kg-BW^{-1}) determined in the invalid IBT study No. F9999.

The other alternate study is discussed in the inhalation section (4.2.1.2). In our opinion, inhalation studies are not appropriate alternates to dietary studies. In this study, there is no definition of dosage or exposure, and therefore no NOEL can be determined; hence, the study is of little use in establishing dose-response criteria.

Table 4-4 summarizes the effects reported in subacute toxicity studies (described in detail in Appendix II.4). As with most organophosphorus pesticides (Hayes 1982), fenitrothion inhibits cholinesterase in erythrocytes, plasma, and brain tissue. Recent subacute studies (Kadota and Miyamoto 1975; Ecobichon and Zelt 1979; Trottier et al. 1980; Durham et al. 1982) have essentially confirmed the data of previous studies. There appears to be a dose-dependant decrease in all cholinesterase activities measured, with the brain cholinesterase showing the greatest depression. Plasma cholinesterase activity apparently has the most rapid recovery time while the brain cholinesterase has the slowest, although the recovery times are also dose-dependant. At a dose as high as 13 mg.kg-BW^{-1}, rats recovered 30 days after withdrawal of fenitrothion (Kimmerle 1962) (see Appendix II.4). In studies where the sex of the animal was reported, females appeared more susceptible to inhibition of cholinesterase activity than did males (Table 4-4).

Table 4-4 Summary of the no-observed-effect levels and the effect levels obtained from subacute studies on fenitrothion (See Appendix II.4 for detail).

Dosage (mg.kg-BW^{-1}.d^{-1})	Species	Route	Duration	Description of Effect	Effect Level (mg.kg-BW^{-1}.d^{-1})	NOEL (mg.kg-BW^{-1}.d^{-1})
0-10	rat	oral		depression of ChE activity		
			90 d	- whole blood	3.7[a]-5.0	0.8[a]
			30-90 d	- plasma	3.7[a]-5.0	0.8[a]-2.5
			30-90 d	- erythrocyte	3.7[a]-5.0	0.8[a]-2.5
			30 d	- brain	2.5	
			13-16 wk	- ocular and systemic symptoms of intoxication	6[a]	-
	dogs	oral	98 d	- inhibition of whole blood, plasma and RBC ChE	9	2
	sheep	oral	60 d	- inhibition of plasma ChE	3	-
	cow	oral	90 d		-	3
	quail	oral	4 wk	- inhibition of whole blood ChE in females	5 ppm	1.5 ppm
				- inhibition of whole blood ChE in males	15 ppm	
10-50	rat	oral	5 d	- impaired pentobarbitone sleeping time and hepatic microsomal monooxygenase activity	50	-
	hens	oral	3-4 wk	- slight BW reduction	16.7	-
				- intoxicating symptoms	33.4	-

[a] Original numbers were reported in ppm diet. They are converted to mg.kg-BW^{-1}.d^{-1} assuming a 0.4 kg rat consuming 16 g of food a day (Altman and Dittmer 1974).

4.2.1.2 Subacute Inhalation Studies

Three major inhalation studies were mentioned in NRCC (1975) (see Appendix II.5 for a review of these studies) but the exposure and results from one of them, Sumitomo (1973), were reported inaccurately. The NOEL for rats is 7 $mg.m^{-3}$ and the apparent lowest level causing observed cholinesterase inhibition in both rats and mice is 15 $mg.m^{-3}$ (Sumitomo 1973). WHO (1973) reported on the effects on man of fenitrothion applied indoors as a residual spray (leaving 2 $g.m^{-2}$ on the wall). Slight to moderate depression of cholinesterase was reported in the spraymen. The third study consisted of a field spraying operation of 5% fenitrothion in Southern Nigeria (Vandekar 1965). This study has been designated as an alternate for an IBT study (F9999) mentioned in Section 4.2.1.1. Spraying lasted for two days and there was significant cholinesterase depression the day after spraying which had disappeared one week later. There was no definition of the exposure or the dosage received in this study. It is questionable if this is an adequate alternate for IBT No. F9999 (see Section 4.2.1.1) which showed a NOEL of 0.1 $mg.kg\text{-}BW^{-1}.d^{-1}$ for cholinesterase inhibition in humans exposed orally to fenitrothion.

A recent inhalation study (nose-only) on rats (Breckenridge et el. 1982) supported the results of Sumitomo (1973). When rats were exposed to concentrations of 6.7, 20.0 and 60.0 mg-fenitrothion. $L\text{-}air^{-1}$, for a 2 h a day for 30 d, a dose-dependant inhibition of plasma, erythrocyte and brain cholinesterases as well as renal and hepatic carboxylases was also observed (see Appendix II.5 for details).

Although it is now believed that in most cases dermal contact is the major exposure route (Wolfe et al. 1972), inhalation exposure may be of prime importance to some groups. For example, it has been suggested that pilots may encounter high inhalation exposure during the aerial application of fenitrothion (McCarthy 1976).

4.2.2 CHRONIC TOXICOLOGY

Of the three chronic studies performed by IBT, one was designated as invalid (see Appendix IV.0). It was a 12-month oral study in dogs[α] (Sumitomo 1975c, IBT No. C1667) for which one of the valid IBT studies, a 2-year oral study in dogs (Sumitomo 1975c, IBT No. 651-09998) was designated as the alternate. The results of the alternate study (Appendix II.6) were very similar to those in the 1-year study.

[α] A subacute 90-day oral study in dogs, which was deemed invalid, was also done (Sumitomo 1975c; IBT No. C9997). This study was not mentioned in NRCC (1975).

As with the subacute studies, recent chronic studies (Kadota et al. 1975a; IBT 1978; Ecobichon et al. 1980) have essentially confirmed the results of the earlier studies mentioned in the NRCC documents (see Table 4-5 for a summary and Appendix II.6 for detail). The effects are essentially similar to those seen in studies of shorter duration (a dose-dependant decrease in all cholinesterase activities measured) except that plasma cholinesterase seems to be the most easily affected and brain cholinesterase the least, the reverse of the subacute effects. The lowest effect levels for cholinesterase inhibition are lower (up to 10-times) in the chronic studies than in the subacute studies. In rats, there appears to be a decrease in body weight gain at the higher doses, e.g. 100 mg.kg-diet^{-1} (4 mg.kg-BW^{-1}) (Sumitomo 1975b).

After the NRCC documents on fenitrothion were published, a chronic study on monkeys was reported by IBT (IBT 1978) and later deemed valid by Health and Welfare Canada (see Appendix II.6). As in the other chronic studies, plasma and RBC cholinesterase were affected at a lower dose than brain cholinesterase. Some questions have been raised about the reliability of the cholinesterase activity values in this study because of wide fluctuations in reported values attributable to the assay procedure (Sumitomo 1984). Electromyograms taken on the test animals showed a minimal but consistent dose-related increase in the duration of insertional activity of the nerve at the tricep muscle. The authors postulated that this could be interpreted as partial denervation of the muscles or an increase in muscle membrane sensitivity. Since no resting spontaneous activity was observed, denervation could not be unequivocally demonstrated and the increase in insertional duration could represent an increase in the excitation of the muscle membrane (IBT 1978). Although this effect was reportedly minimal, histopathological photographs were of low quality making it difficult to see anything (Sumitomo 1984).

4.3 NEUROTOXICOLOGY

The section on neurotoxicity in NRCC (1975) is based on an invalid IBT study (Sumitomo 1972d, IBT No. 8580-09445), for which Health and Welfare Canada has named five alternate or replacement studies (see Appendix IV.0). Two of these alternate studies (Carshalton 1962; Kimmerle 1962) were included in the FAO/WHO (1970) review, which is appended to NRCC (1975). Table 4-6 is a summary of the studies on the neurotoxic effects of fenitrothion (reviewed in detail in Appendix II.7).

One of the replacements studies submitted by Sumitomo Chemical Co. (1977) examined hens administered Sumithion technical at 500 mg.kg-BW^{-1} twice at a 3-week interval (see Appendix II.7). Three of sixteen hens died after the first dose and three more died after the second dose. Most of the remaining hens exhibited positive paralytic signs (loss of leg coordination and balance) shortly after both doses but the symptoms disappeared 4-9 days post-treatment.

Table 4-5. Summary of the no-observed-effect levels and the effect levels obtained from chronic studies on fenitrothion (See Appendix II.6 for details).

Dosage (mg.kg-BW^{-1}.d^{-1})	Species	Route	Duration	Description of Effect	Effect level (mg.kg-BW^{-1}.d^{-1})	NOEL (mg.kg-BW^{-1}.d^{-1})
0-10	rat	oral	63-104 wk	depressed ChE		
				- plasma	0.2[α]-5.0	0.1[α]-1.0
				- RBC	0.4[α]-5.0	1.0
				- brain	0.4[α]-5.0	1.0
				- renal CE	5.0	-
				- liver CE	0.5	-
				- decreased body weight in males	4[α]	-
				- temporary deterioration of general condition and loss of weight	10-11	-
				- slight to marked mammary cystic glandular dilation in females	4[α]	-
				- no effects seen in hematology, urinalysis or gross pathology	-	6-11
	dog[β]	oral	24 mo	- inhibition of plasma ChE	0.9[γ]	-
				- no effects on blood chem., hematology, urinalysis and gross pathology and histology	-	6.0[γ]
	monkey[β]	oral	24 mo	depressed ChE		
				- plasma	2.0	0.5
				- RBC	2.0	0.5
				- brain	-	2.0
				- minimal but consistent dose-related increase in the duration of the insertional activity in the EMG	0.1	-

[α] Original numbers were reported in ppm diet. They were converted to mg.kg-BW^{-1}.d^{-1} assuming a 0.4 kg rat consuming 16 g of food a day (Altman and Dittmer 1974).

[β] Based on one study only.

[γ] Original numbers were reported in ppm diet. They are converted to mg.kg-BW^{-1}.d^{-1} assuming a 15 kg dog consuming 450 g of food a day (Altman and Dittmer 1974).

Table 4-6. Summary of the no-observed-effect levels and the effect levels obtained from neurotoxicity studies on fenitrothion (See Appendix II.7 for details).

Dosage ($mg.kg\text{-}BW^{-1}.d^{-1}$)	Species	Route	Duration	Description of Effect	Effect level	NOEL
					($mg.kg\text{-}BW^{-1}.d^{-1}$)	
0-10	rat[a]	oral	single dose	- in testing the avoidance reflex action, the number of positive conditioned responses decreased	4	-
10-50	rabbit[a]	oral	12 wk	- decrease in conduction velocity of the sciatic nerve - ChE inhibition - some destruction of the myelinated fibres of the sciatic nerve - signs of poisoning	10	-
5-500	hen	oral	single dose	- motor ataxia, decreased spontaneous motor activity, irregular respiration - some evidence of scattered degenerated fibres in the spinal cord	400-500	-

[a] Based on only one study.

The other replacement study, Sumitomo (1976), was also reported in Kadota et al. (1975b) (see Appendix II.7). In a preliminary test using doses of 250, 500 and 1000 mg.kg-BW^{-1}, the LD_{50} for hens was observed to be 500 mg.kg-BW^{-1}. The LD_{50} was administered twice to hens, again at a 3-week interval. Five of sixteen birds died in the first 24-48 hours and the toxic symptoms (motor ataxia, decrease of spontaneous motor activity and irregular respiration) appeared early and disappeared shortly afterwards as in the Sumitomo (1977) study. After the second dose, the symptoms reappeared in the surviving hens.

Lehotsky and Ungvary (1976) found that fenitrothion altered the conditioned avoidance reflex in male rats (see Appendix II.7). In rats given 100 mg.kg^{-1} once orally (not specified as to mg.kg-BW^{-1} or mg.kg-diet^{-1}), the number of conditioned responses dropped to 54% within two hours of treatment (compared with 95% in controls) although the trend of extinction of responses was slower than in the control group.

Lehotsky and Ungvary (1976) also treated rabbits orally with fenitrothion, at dosages of 10 mg.kg^{-1}.d^{-1} for 8 weeks or 25 mg.kg^{-1}.d^{-1} for 4 weeks (unspecified whether per BW or per diet). The conduction velocity of the sciatic nerves decreased at both doses and histopathological examination revealed the destruction of the myelinated fibres of the sciatic nerve in only the rabbits dosed at 10 mg.kg^{-1}. This supports the hypothesis that neurotoxic effects are more likely to be seen following long-term exposure. The animals dosed at 10 mg.kg^{-1} showed no gross signs of intoxication although whole blood cholinesterase levels were approximately 50% of controls. The rabbits treated at 25 mg.kg^{-1} showed marked signs of poisoning although no pathological changes were reported. The results are contrary to those of Fullerton and Barnes (1966) who showed that marked changes in nerve velocity were observed only after drastic pathological changes had occurred. The authors believe that nerve conduction velocity may be an earlier indicator of neurotoxic effects. It should be noted that both the results and experimental design of the Lehotsky and Ungvary (1976) study are questioned (Ecobichon 1983).

The statement in NRCC (1975) was that no neurotoxic effects were observed in hens; this was based on the very sparse literature available at that time. The more recent studies indicate a need for this topic to be examined again, utilizing more up-to-date techniques.

4.3.1 DELAYED NEUROTOXICOLOGY

Some organophosphorus compounds have shown delayed neurotoxic effects and although the mechanism is not fully understood, apparently it is not connected to inhibition of the cholinesterase enzyme. Delayed neurotoxicity is characterized by leg weakness approximately 8-14 days after exposure and by irreversible demyelination of both the central and peripheral nervous systems (Eto 1974). The degenerative lesions occur

at the distal portion of the long axons of the spinal cord and peripheral nerves such as the sciatic nerve.

Cats and hens have been shown to be the most sensitive indicators of neurotoxic effects. Since the hen is relatively similar to humans in response to poisoning incidents (NRCC 1982), it is usually the species chosen for neurotoxicity tests. TOCP[α], the best known example of a neurotoxic organophosphate, is often used as a positive control in these tests.

Based on its structure-activity relationship to TOCP and other delayed neurotoxic compounds, fenitrothion would not be expected to cause delayed neurotoxic effects (for a more detailed discussion, see Eto 1974).

It has been suggested that as the length of exposure to a neurotoxic compound increases, the effects may be observed at lower dosages (NRCC 1977a,b). Since most delayed neurotoxicity studies of fenitrothion have been based on only one or two applications, this question cannot be answered with respect to fenitrothion.

The alternate and replacement studies mentioned above (Section 4.3) also include tests for delayed neurotoxic effects. The common symptoms of delayed neurotoxicity, delayed leg weakness and degeneration of the sciatic nerves and spinal cord (Eto 1974), were not reported in Sumitomo (1976, 1977) although acute neurotoxic effects were reported. Neither Carshalton (1962) nor Kimmerle (1962) reported paralysis although a few scattered degenerated fibres were found in the spinal cord of one hen (Carshalton 1962). Unpublished studies by Ecobichon (1983), in which hens were treated with 500 mg.kg-BW^{-1}.d^{-1} of fenitrothion, reported no alterations in physiological, biochemical or morphological parameters that would be indicative of delayed neurotoxicity.

4.4 REPRODUCTION AND TERATOGENICITY

The reproductive effects of fenitrothion in laboratory animals were not well studied in 1975 and only one additional study has been published since then. Three of the earlier studies were conducted by IBT and have been reviewed and designated as valid by Health and Welfare Canada. Table 4-7 gives a summary of the reproductive studies in laboratory animals (see Appendix II.8 for more detail).

Although no teratogenic or reproductive effects have been reported in rabbits, ducks and quail, rats dosed at 4 mg.kg-BW^{-1}.d^{-1}

[α] TOCP - tri-o-cresyl phosphate.

Table 4-7. Summary of the no-observed-effect levels and the effect levels obtained from reproduction studies[α] on fenitrothion (See Appendix II.8 for details).

Species	Route	Duration	Description of Effect	Effect level	NOEL
				($mg.kg\text{-}BW^{-1}.d^{-1}$)	
rat	oral	3 generation	- reduced BW in parents - decreased number and weight of weanlings	4[β]	0.4[β]
rabbit	oral	12 d		-	1
duck	oral	1 generation		-	100 $mg.kg\text{-}diet^{-1}$
quail	oral	1 generation		-	10 $mg.kg\text{-}diet^{-1}$
chicken (eggs)	inoculation into the yolk space	1-8 d	- malformations (i.e. curled toe), leg weakness, abnormal gait - reduced hatchability	1×10^{-4}[γ] mg	-

[α] All entries based on one study each.

[β] Original numbers were reported in ppm diet. They are converted to $mg.kg\text{-}BW^{-1}.d^{-1}$ assuming.a 0.4 kg rat consuming 16 g of food a day (Altman and Dittmer 1974).

[γ] Dose was 1% fenitrothion in 0.1 mL of water.

showed a decrease in the number and weight of weanlings (Hazelton Lab. 1974). This dosage is less than one-hundredth the LD_{50} for rats (Table 4-2). A study published subsequent to the NRCC (1975) report noted that when chick embryos were inoculated with fenitrothion by injecting 0.1, 0.5 and 1% in 0.1 mL of water (containing 0.0001, 0.005 and 0.001 mg fenitrothion) into the yolk space, there was a decrease in the hatchability rate at all doses (Paul and Vadlamudi 1976). Malformations (curled toe), leg weakness and abnormal gait were also evident in the chicks. The embryos appeared to be much more susceptible during the earlier part of the incubation period. The significance of this type of study in relation to mammalian reproduction is unknown.

4.5 MUTAGENIC ACTIVITY

In NRCC (1975), it was stated that fenitrothion had been found to have "little mutagenic" potential under the explicit conditions tested. This was based on the very sparse literature available at that time, none of which involved IBT studies. Miyamoto (1977) of Sumitomo Chemical Company reported in NRCC (1977a) that neither fenitrothion nor its metabolites were mutagenic when tested on several Salmonella typhimurium strains. He also reported that no statistically significant increases in dominant lethal effects were found in rats or mice although there were sporadic nonstatistically significant increases in rats (see Table 4-8 for a summary of mutagenicity and Appendix II.9 for details).

Several reports have been published since NRCC (1975). In a 4-generation study on rats, Benes et al. (1975) found no increases in the number of chromosome breaks or exchanges or in the frequency of dominant lethals. An effect may have been masked because the authors ignored all animals where all of the fetuses were resorbed. Degraeve et al. (1980) pointed out that dominant lethal mutations cannot be observed if the compound being tested causes pre-implantation loss. In testing several OP insecticides in the mouse (DLM), no increase in the percentage of dead implants were found. However, the numbers of pre-implantation losses increased with some chemicals (not fenitrothion). The same chemicals showed a strong mutagenic effect in yeast (forward mutations ad 6).

In one of a series of studies on the mutagenicity of several pesticides, Njagi et al. (1980) reported that fenitrothion was negative in a test for recessive lethality in the X-chromosome using the fruit fly, Drosophila melanogaster, as the test organism. In studies with the bean seedling, Vicia faba, evidence of mitotic inhibition, formation of pycnotic nuclei and premature chromosome condensation was found (Gopalan and Njagi 1979; Njagi and Gopalan 1981).

Table 4-8. Summary of mutagenic effects of fenitrothion.

Species	Type of Test (dose in mg.kg-diet^{-1})	Route	Description of effect
rat	(3 gen.) DLT[a] (10, 40 & 80)	oral (diet)	-no effects seen
rat	(4 gen.) DLT[a] (0, 10, 40, 80)	oral (diet)	-no increase in frequency of DL
rat	DLT (2, 7, 20)	oral (diet)	-sporadic increase in DL (not stat. significant)
mouse	DLT (20 or 200 mg.kg-BW^{-1})	oral (diet)	-no stat. significant effect
mouse and Salmonella typhimurium G 46	host-mediated assays (100 & 200 mg.kg-BW^{-1})	oral or intramuscular	-no increased mutation frequency
S. typhimurium TA 100 & TA 98	fenitrothion & major metabolites (dissolved in DMSO, 1, 10, 100 and 1000 µg/plate)		-m-hydroxymethyl fenitrothion gave slightly larger number (2-3-fold) of revertant colonies
S. typhimurium TA 1535, TA 1537, TA 1538	Ames Test (0.01-10 mg fenitrothion/disc tested)		-negative in Ames Test for reverse mutation and DNA damage
Escherichia coli K12 & coli-phage			-"little" mutagenic and radiometic potential
Drosphila	Muller-5 genetic test		-no evidence of recessive lethality in the X-chromosome
Vicia faba	examined chromosome aberrations (50% AI 100 ppm for 120 min)		-mitotic inhibition, formation of pycnotic nuclei and premature chromosome condensation

[a] DLT - dominant lethal test.

Appendix I.0 NOTICE ON SUBCOMMITTEE MONOGRAPHS CONTAINING INDUSTRIAL BIOTEST MATERIAL

Picloram: The Effects of Its Use as a Herbicide on Environmental Quality. 1974. NRCC No. 13684

Endosulfan: Its Effects on Environmental Quality. 1975. NRCC No. 14098

Fenitrothion: The Effects of Its Use on Environmental Quality and Its Chemistry. 1975. NRCC No. 14104

Fenitrothion: The Long Term Effects of Its Use in Forest Ecosystems - Current Status. 1977. NRCC No. 15389

Proceedings of a Symposium on Fenitrothion: The Long-Term Effects of Its Use in Forest Ecosystems. 1977. NRCC No. 16073

Bacillus thuringiensis: Its Effects on Environmental Quality. 1976. NRCC No. 15385

Polychlorinated Biphenyls: Biological Criteria for an Assessment of Their Effects on Environmental Quality. 1978. NRCC No. 16077

Ecotoxicology of Chlorpyrifos. 1978. NRCC No. 16079

Carbofuran: Criteria for Interpreting the Effects of Its Use on Environmental Quality. 1979. NRCC No. 16740

Approximately four years ago, it was recognized by Canadian and U.S. authorities that irregularities existed in some reports of animal studies carried out by Industrial Biotest Laboratories Incorporated of Northbrook, Illinois. A cooperative effort of Health and Welfare Canada and the U.S. Environmental Protection Agency to validate the studies indicates that safety evaluations of 97 pesticides are supported wholely or in part by studies from this contract laboratory. Audits of the individual studies indicate that a significant portion are invalid. These agencies have requested new studies when information central to the assessment of human safety is "suspect". Specific details of the concerns that form the basis of these requests are unavailable.

The following monographs of the NRC's Subcommittee for Pesticides and Industrial Organic Chemicals are affected: picloram, endosulfan, fenitrothion, Bacillus thuringiensis, polychlorinated biphenyls, chloropyrifos and carbofuran. These documents contain some toxicological studies conducted by IBT, which must be considered as "suspect" in light of the present situation. Hence, until the matter of the validation has been clarified, particular caution should be maintained to avoid the use of criteria developed on the basis of the IBT material. As additional information on the situation and replacement studies become available, the Subcommittee intends to review the need for updates of individual monographs.

APPENDIX II.0

Summary of the Toxicology Studies on Fenitrothion

Appendix II.1. Summary of acute dietary studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})[α]	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[R])	Presence[γ] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Nosal and Hladka (1968)	human [24] (sex unspecified)	fenitrothion (98 & 100%) in olive oil -doses: 2.5, 5, 10, 15 & 20 mg (0.042 -0.33 mg.kg-BW^{-1})	oral (capsule)	Alternate for IBT No. F9999	NRCC (1975) (p. 129) NRCC (1977a) (p. 419)	-almost all p-nitro-m-cresol (NC) is discharged within the 1st 24 h -quantity of NC eliminated in direct ratio to the size of the dose -plasma and RBC ChE activity all within normal range except 1 person who showed low PChE and was ill for 1-2 h after treatment			-age of test subjects not given
Keith and Mulla (1966)	mallard duck [6]	fenitrothion (tech.) in corn oil -doses: 25-200 -observed for 10 d	oral (in capsule)	-could be an alternate for IBT No. J9992	NRCC (1975) (p. 65)	-states LD_{50} (10-d) as 100-150 mg.kg-BW^{-1}			-no data given on sex of birds -only used 6 animals -exact doses not clear
UPDATE IBT (1971g)	mallard duck	Sumithion (tech. - 97.1%)	-	INVALID (IBT No. J9992)	-				
Kadota and Miyamoto (1975)	Japanese quail [8 male; 8 female]	Sumithion (tech. - 97%) in 10% Tween 80 -doses: 67.8, 95, 133, 186 & 260	oral	-could be alternate for IBT No. J9992	-	-states LD_{50}s (2-wk) as 115 (80-166) and 140 (105-186) mg.kg-BW^{-1} for males and females, respectively (95% confidence limits) -dec. in spontaneous motor activity and slight motor ataxia at 67.8 mg.kg-BW^{-1} and above -severity of symptoms followed dose-response	-	67.8	-method of oral administration not given -reports recovery time for a dose of 260 mg.kg-BW^{-1} but all animals died at that dose

II.1. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})[α]	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[β])	Presence[γ] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
IBT (1971h)	pheasant [30 male; 30 female]	Sumithion (tech. - 97.1%) -doses: 0, 14.7, 21.5, 31.6, 46.4 & 68.1	oral (gavage)	Valid (IBT No. J9993)	-	-LD_{50} (21-d) stated as 34.5 mg.kg-BW^{-1} -min. lethal dose 14.7 mg.kg-BW^{-1} (40% dead)	-	14.7	-no confirmation of identity of test material -inaccurate dosing (incorrect syringe) -no concurrent controls -solvent not specified -random dose-response in females
Kadota et al. (1975b) or Sumitomo (1976)	hen [18]	Sumithion (tech. - 97.2%) in 10% Tween 80 -doses: 250, 500, 1000 -observed for 5 wk	oral (gavage)	-	-	-calculated LD_{50} (10-d) as 500 mg.kg-BW^{-1} -leg weakness and lack of leg coordination observed at 250 mg.kg-BW^{-1} and above	-	250	-only dosed at 3 doses over a very wide range to get the LD_{50}
IBT (1971i)	beagle dog [16]	Sumithion (tech.- 97.1%) -doses: 0.0-4640.0	oral (capsule)	Valid (IBT No. J9994)	-	-min. observed lethal dose stated as 681 mg.kg-BW^{-1} -min. emetic dose 215 mg.kg-BW^{-1} -clonic convulsions and ataxia reported at 316 mg.kg-BW^{-1} and above	-	215	-no confirmation of identity of test material -missing data in final report -no information on breed or health of dogs in raw data -emesis occurred

II.1. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})[α]	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[β])	Presence[γ] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
IBT (1971c)	mallard duck [30 male; 30 female]	Sumioxon pure in corn oil -doses: 0, 10.00, 14.70, 21.60, 31.75 & 46.67	oral (gavage)	Valid (IBT No. J102)	-	-LD_{50} (21-d) reported as 12.50 mg.kg-BW^{-1} (95% confidence limits, 8.06-19.38) -40% dead at lowest dose; 10.00 mg.kg-BW^{-1}	-	10.0	-no information on origin, age or source of birds -no raw data on food consumption
IBT (1971d)	pheasant [30 male; 30 female]	Sumioxon pure in corn oil -doses: 0, 3.16, 4.64, 6.81, 10.00 & 11.47	oral (gavage)	Valid (IBT No. J103)	-	-LD_{50} (21-d) calculated as 10.60 mg.kg-BW^{-1} (95% confidence limits, 8.55-13.14) -increased mortality at 6.81 mg.kg-BW^{-1} (30% dead)	-	6.81	-source of test material not specified -no information on origin, age or source of birds -no raw data on food consumption
IBT (1971a)	beagle dog [8]	Sumioxon pure -doses: 10.0, 14.7, 21.5, 31.6, 46.4, 68.1, 100.0 & 147.0	oral (capsule)	Valid (IBT No. J100)	-	-all animals exhibited salivation, diarrhea and ataxia within 3 h -animals receiving > 68 mg.kg-BW^{-1} died in 1-2 h		10	-no details of oral administration given -proposed protocol of study not available
IBT (1971e)	mallard duck [7 male; 6 female]	p-nitro-m-cresol (99.6% pure) -1.00, 1.47, 2.15, 3.16, 4.64 & 6.81 g.kg-BW^{-1}	oral (capsule)	Valid (IBT No. J104)	-	-min. emetic dose reported as 1.47 g.kg-BW^{-1} -min. lethal dose reported as > 6.81 g.kg-BW^{-1}	-	1470	-no information on origin, age or source of ducks -protocol of study not available -final report states pathology was performed but no animals died or were autopsied in the study

II.1. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})[α]	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[X])	Presence[Y] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
IBT (1971f)	pheasant [30 male; 30 female]	p-nitro-m-cresol (99.6% pure) -doses: 0, 1.00, 1.47, 2.15, 3.16 and 4.64 g.kg-BW^{-1}	oral (capsule)	Valid (IBT No. J105)	-	-LD_{50} stated as > 4.64 g.kg-BW^{-1} (no emesis reported) -min. lethal dose 4.64 g.kg-BW^{-1}		4.64	-no information on origin, age or source of birds -emesis not mentioned
IBT (1971b)	beagle dog [4 male; 3 female]	p-nitro-m-cresol (99.6% pure) -doses: 0.215, 0.316, 0.464, 0.681, 1.00, 1.47 & 4.64 g.kg-BW^{-1}	oral (capsule)	Valid (IBT No. J101)	-	-min. emetic dose > 0.681 g.kg-BW^{-1} and < 1.00 g.kg-BW^{-1}			-no information on "preconditioning", origin, age or source of dogs -results from 1 animal (highest dose level) were not reported -emesis occurred in 3 of 8 animals at higher doses
Bioresearch[6] (1982a) #50322	rat (albino) a) [12 male; 12 female] b) [60 male; 60 female]	fenitrothion tech. (14% w/w) with Cyclosol 63 (24%) and Triton X114 (3%) in distilled water (59%) doses: a) Range finding study: 1000, 2500, 5000, 1750, 3500 and 4200 b) LD_{50} study: 2500, 2871.7, 3298.8, 3789.3, 4352.8 and 5000.0 in a dose volume of 10 mL.kg-BW^{-1} -observed for 14 d	oral (gavage)	-	-	-signs of toxicity included hunched back, lacrimation, ptyalism, perineal staining, epistaxis, lethargy, ataxia, reduced motor activity, tremors, dyspnea and bradypnea -surviving animals normal by 7 d -LD_{50}s stated as: 2900 mg.kg-BW^{-1} (406 mg-AI.kg-BW^{-1}) for females, 3400 (476) for males and 3400 (476) for combined sexes -10% mortality at lowest dose level- 2500 mg.kg-BW^{-1} -mortality generally occurred over 1st 3 d	-	2500 (350 mg-AI. kg-BW^{-1})	-assumed that signs of toxicity occurred at all dose levels but not stated

II.1. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})[a]	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[x])	Presence[y] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Bioresearch (1982a) (Cont'd) #50321	rat (albino) [as above]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (24%) and Triton X100 (3%) in distilled water (59%) doses: a) Range finding study: as previous b) LD_{50} study: 2500.0, 2773.3, 3076.5, 3412.9, 3786.1, 4200 -observed for 14 d	oral (gavage)	-	-	-signs of toxicity as above, normal by 8 d -LD_{50}s stated as: 3150 mg.kg-BW^{-1} (441 mg-AI. kg-BW^{-1}) for females, 2750 (385) for males and 3100 (434) for combined sexes -25% mortality at 2500 mg.kg-BW^{-1} -mortality generally occurred over 1st 3 d		2500 (350 mg-AI. kg-BW^{-1})	-as above
#50273	rat (albino) [as above]	-fenitrothion tech. (14% w/w) with Triton X114 (14%) in distilled water (72%) doses: a) Range finding study: 1000, 2500, 5000, 500, 1750, 3500 b) LD_{50} study: 2500.0, 2871.7, 3298.8, 3789.3, 4352.8, 5000.0 -observed for 14 d	oral (gavage)	-	-	-signs of toxicity generally as above, normal by 5 d -LD_{50}s stated as: 3400 mg.kg-BW^{-1} (476 mg-AI.kg-BW^{-1}) for females, 3570 (500) for males and 3550 (497) for combined sexes -5% mortality at 2500 mg.kg-BW^{-1} -mortality generally occurred over 1st 2 d		2500 (350 mg-AI. kg-BW^{-1})	-as above

II.1. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})[α]	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[β])	Presence[γ] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Bioresearch (1982a) (Cont'd) #50272	rat (albino) [as above]	-fenitrothion tech. (14% w/w) with Triton X100 (14%) in distilled water (72%) doses: a) Range finding study: as previous b)LD_{50} study: 4000.0, 4337.9, 4704.3, 5101.7, 5532.6, 6000.0 -observed for 14 d	oral (gavage)	-	-	-signs of toxicity included piloerection, hunched back, reduced motor activity, lethargy, dyspnea, tremors -normal by 6 d -LD_{50}s stated as: 6200 mg.kg-BW^{-1} (868 mg-AI.kg-BW^{-1}) for females, 5400 (756) for males and 5650 (791) for combined sexes -10% mortality at 4000 mg.kg-BW^{-1} -mortality generally occurred within the first 24 h		4000 (560 mg-AI. kg-BW^{-1})	-as above

[α] Acute studies all have a single dose.

[β] No IBT involvement, to our knowledge.

[γ] Studies examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[δ] The studies by Bioresearch were received by the authors after the Associate Committee review.

Appendix II.2. Summary of acute dermal and ocular studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[4])	Presence[3] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Kohli et al. (1974)	rat	fenitrothion a) single dose of 0.1 mL (132 mg)	dermal	-	NRCC (1975) (p. 80)	a) readily absorbed, reached a peak plasma concentration (47 ug.mL^{-1}) in 8 h -45% absorbed within 24 h -decrease in ChE varied with fenitrothion level in blood			
		b) 2 doses of 0.5 mL (650 mg) 24 h apart				b) complete inhibition of ChE in whole blood -animals were dying and exhibited fine to coarse tremors			
Sumitomo (1972e)	rabbit	fenitrothion	eye irritation	INVALID (IBT No. 601-04051)	NRCC (1975) (p. 80)				
UPDATE									
Sumitomo (1981)	rabbit-male albino [9]	Sumithion (tech. - 96.5%) a) 0.1 mL on one eye of each rabbit -untreated eyes served as controls -washed treated eyes of 3 animals 30 s after application	eye irritation)	Replacement for IBT No. 601-04051	-	a) no ocular lesions in washed eyes -slight hyperemia found in conjunctivas of the group with unwashed treated eyes that disappeared 48 h after application			
	[6]	b) 0.5 mL to abraded and intact skin	skin irritation			b) no lesions were observed			-vehicle not mentioned
Ecobichon et al. (1977)	human-female	fenitrothion and equal parts (1.5 cc) Aerotex 3470, Toximul MP-8 + Atlox 3409F and corn oil (18 oz)	dermal and inhalation	-	-	-toxic poisoning symptoms (nausea, blurred vision + muscular weakness) and depressed ChE (AChE + plasma PChE) -muscular effects lasted several months			-case study-accidental poisoning -exposure unknown

Appendix II.2. (Cont'd)

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions		Comments
						NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	
Bioresearch[γ] (1982b) #50328	rabbit (albino) [5 male; 5 female]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (24%) and Triton X114 (3%) in distilled water (59%) dose: 2000 mg.kg-BW^{-1} (280 mg-AI.kg-BW^{-1}) applied to abraded skin on the dorsal surface, covered for 24 h -observed for 14 d	dermal	-	-	-mild to moderate erythema and/or edema -no mortality		-no control -age of animals not given
#50327	rabbit (albino) [5 male; 5 female]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (24%) and Triton X100 (3%) in distilled water (59%) dose: as above	dermal	-	-	-mild to moderate erythema and/or edema -no mortality		-as above
#50285	rabbit (albino) [5 male; 5 female]	-fenitrothion tech. (14% w/w) with Triton X114 (14%) in distilled water (72%) dose: as above -observed for 15 d	dermal	-	-	-transient edema and mild to moderate erythema -no mortality		-as above
#50284	rabbit (albino) [5 male; 5 female]	-fenitrothion tech. (14% w/w) with Triton X100 (14%) in distilled water (72%) dose: as above -observed for 15 d	dermal	-	-	-mild erythema -no mortality		-as above

Appendix II.2. (Cont'd)

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Bioresearch[γ] (1982c) #50326	rabbit-male albino [6]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (24%) and Triton X114 (3%) in distilled water (59%) dose: 0.5 mL (0.07 mL AI) applied to abraded and intact shaven skin with dermal pads -covered for 24 h -observed for 9 d	skin irrita-tion	-	-	-sporadic occurrence of slight erythema at both abraded and intact sites -authors judge test material to be a "non irritant" to rabbit skin			-no controls evident -age of animals not given
#50325	rabbit-male albino [6]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (14%) and Triton X100 (3%) in distilled water (59%) dose: as above -observed for 8 d	skin irrita-tion	-	-	-mild erythema and/or edema seen at both abraded and intact sites at 24 h on all animals, all recovered by 7 d -authors judge test material to be "virtually nonirritant" to rabbit skin			-as above
#50281	rabbit-male albino [6]	-fenitrothion tech. (14% w/w) with Triton X114 (14%) in distilled water (72%) dose: as above -observed for 7 d	skin irrita-tion	-	-	-very slight erythema at both abraded and intact sites on most animals at 24 h -most sites were normal by 4 d, all by 6 d -authors judge test material to be a "non-irritant" to rabbit skin			-as above
#50280	rabbit-male albino [6]	-fenitrothion tech. (14% w/w) with Triton X100 (14%) in distilled water (72%) dose: as above -observed for 6 d	skin irrita-tion	-	-	-slight erythema and/or edema observed in a few sites in 3/6 animals -all normal by 6 d -authors judge test material to be a "non-irritant" to rabbit skin			-as above

Appendix II.2. (Cont'd)

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Bioresearch[γ] (1982d) #50324	rabbit-male albino [9]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (14%) and Triton X114 (3%) in distilled water (59%) -0.1 mL (0.014 mL-AI) on one eye of each rabbit -untreated eyes served as the controls -washed treated eyes of 3 animals for 1 min 20-30s after instillation -observed for 8 d	eye irritation	-	-	-very mild conjunctivitis, pannus and mild purulent discharge in unwashed eyes at 24 h -completely recovered by 7 d -authors conclude test material is "virtually" a non-ocular irritant			-age of animals not given
#50323	rabbit-male albino [9]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (14%) and Triton X100 (3%) in distilled water (59%) -dosing as above -observed for 7 d	eye irritation	-	-	-pannus noted in 2 washed eyes at 24 h and purulent discharge in 1 washed eye at 7 d -in unwashed eyes: -corneal opacity noted in 1/6 (gone by 72 h), mild and transient conjunctivitis in 4/6 (gone by 7 d) and mild pannus, conjunctival blistering, purulent discharge in 6/6 (reversed by 72 h) -authors concluded that the test material is a "very mild" ocular irritant			-as above

Appendix II.2. (Cont'd)

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Bioresearch (1982d) (cont'd) #50334	rabbit-male albino [9]	-fenitrothion tech. (14% w/w) with Triton X114 (14%) in distilled water (72%) -dosing as above -observed for 15 d	eye irrita-tion	-	-	-mild to moderate opacity of cornea noted in unwashed eyes of 4 animals (2 recovered by 48 h, 1 by 4 d and 1 not until 13 d) -slight redness of conjunctivae in all treated eyes except 2 washed eyes -mild to moderate chemosis in 5/6 of unwashed group -corrosive action in all animals of unwashed group -authors conclude that the test material is a "mild" ocular irritant			-as above
#50333	rabbit-male albino [9]	-fenitrothion tech. (14% w/w) with Triton X100 (14%) in distilled water (72%) -dosing as above -observed for 15 d	eye irrita-tion	-	-	-very mild pannus noted in 1 washed eye -in unwashed eyes: mild opacity, mild to moderate redness, mild to severe chemosis and mild to severe pannus noted in all animals + all but 1 animal was normal by 13 d -authors conclude that the test material is a "mild" ocular irritant			-as above -HWC (1984) noted that because of the extent and severity of the reactions, this formulation should be considered a moderate to severe irritant

[α] No IBT involvement, to our knowledge.

[β] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[γ] Bioresearch studies were received by the authors after Associate Committee review.

Appendix II.3. Summary of acute potentiation studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Dubois and Kinoshita (1963)	rat-female	-fenitrothion in combination with the following OPs: parathion, parathion-methyl, demeton, disulfoton, malathion, EPN, azinphos-methyl, carbophenothion, mevinphos, dioxathion, schradan, ethion, diazinon, Folex, coumaphos and fenchlorophos as well as the carbamate carbaryl	i.p.	-	NRCC (1975)[γ] (p. 126)	-no sign of potentiation			
Braid and Nix (1968)	rat-male and female	-mixtures of fenitrothion and phosphamidon	oral	-	NRCC (1975)[γ] (p. 126)	-marked potentiation in both males and females -in females the potentiation effect diminished as the conc. of fenitrothion increased			
UPDATE Ramakrishna and Ramachandran (1978)	mice-[groups of 20]	-LD_{50} of fenitrothion 1st determined to be 980 mg.kg-BW^{-1} -fenitrothion (95% pure) in ground nut oil administered sequentially with malathion (an interval of 18 h) -doses: 12.5, 25, 50, 100 and 200 -malathion B esterase and the phenyl acetate esterase activities of the liver and the AChE activities of the brain were determined	i.p.	-	-	-initial lag in AChE inhibition, even when fenitrothion inhibits CE by ~ 65%, there is hardly any AChE inhibition -fenitrothion is a powerful synergist - at 0.025 and 0.05 LD_{50}s (25 & 50 mg.kg-BW^{-1}), it brings the LD_{50} of malathion to 355 and 288 mg.kg-BW^{-1} respectively (from 1223 mg.kg-BW^{-1}) ∴ fenitrothion is a potentiator of malathion at sublethal dosages			-sex, strain, age and origin of mice not given

[α] No IBT involvement, to our knowledge.

[β] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[γ] The conclusions on these studies are those found in FAO/WHO (1970).

Appendix II.4. Summary of subacute dietary studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	Comments
Kimmerle (1962)	rat - male	fenitrothion -dose: 13 -28-d study	oral	-	NRCC (1975)[γ] (p. 128)	-RBC ChE showed severe depression, recovered by 30 days after withdrawal of fenitrothion			
Carshalton (1964)	rat - male	fenitrothion -doses: 5, 10 & 20 mg.kg-diet^{-1} for an unspecified time period	oral (diet)	-	NRCC (1975)[γ] (p. 128)	-10 mg.kg-diet^{-1} - slight depression of RBC ChE after 5 wk - recovery 2 wk after withdrawal -20 mg.kg-diet^{-1} - depression of RBC and brain ChE, recovery in brain incomplete 2 wk after withdrawal			
Cooper (1966)	rat	fenitrothion -90-d study	oral (diet & drinking water)	-	NRCC (1975)[γ] (p. 128)	-inhibition of plasma, RBC and whole blood ChE	20 mg.kg^{-1} in the diet & 10 mg.kg^{-1} in the drinking water	92.8 mg.kg^{-1} in the diet and 46.4 mg.kg^{-1} in drinking water	
Sumitomo (1972b)	sheep [2]	Sumithion (tech.) -dose: 3 -60-d study	oral	-	NRCC (1975) (p. 79)	-significant drop in plasma ChE in one animal on day 7 only			
Sumitomo (1972b)	cattle	fenitrothion -doses not specified -3-mo study	unspecified	-	NRCC (1975) (p. 78)	-no effect on plasma ChE	3	-	
Johnsun and Bowman (1972)	cattle	Sumithion -100 mg.kg-diet^{-1} -28-d study	oral (diet)	-	NRCC (1975) (p. 78)	-no effect on whole blood ChE	100 mg.kg-diet^{-1}	-	

II.4. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	Comments
Leuck et al. (1971)	cattle (lactating)	fenitrothion -dose: 0.66 -8-wk study	oral	-	NRCC (1975) (p. 78)	-traces of amino analogue in milk at dose as low as 0.66 mg.kg-BW^{-1}.d^{-1} -whole blood ChE, silage intake and milk production not affected at this level			
Sumitomo (1975c)	dog	Sumithion -90-d study	oral (diet)	INVALID[δ] (IBT No. C9997)	-				
Cooper (1966)	dog	fenitrothion -doses: 0, 2, 9 and 40 -study up to 98-d in duration	oral	-	NRCC (1975)[γ] (p. 127)	-at 9 mg.kg-BW^{-1}.d^{-1} - slight depression in whole blood, plasma and RBC ChE after 60 d -at 40 mg.kg-BW^{-1}.d^{-1} - moderate depression of above after 29 days, also toxic symptoms	2	9	
IBT (1972)	human	fenitrothion -2 or 3 mo study	oral	INVALID (IBT No. F9999)	NRCC (1975) (p. 79)				
UPDATE Fukami (1976) (Abstract only)	rat[ε]	fenitrothion -doses: 150 & 300 mg.kg-diet^{-1} for 13 and 16 wk respectively	oral (diet)	-	-	-rats showed dose-related ocular and systemic symptoms of intoxication and reduction of serum ChE activity	-	150 mg.kg-diet^{-1}	-Abstract only

II.4. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	Comments
Ecobichon and Zelt (1979)	rat[ε] -weanling male	fenitrothion (tech.- 97%) in peanut oil -dose: 50 -5-d study	oral (gavage)	-	-	-inhibition of RBC and brain AChE, plasma PChE and hepatic and renal CE -recovery of PChE was rapid but slow for others -fenitrothion impaired pentobarbitone sleeping time and hepatic microsomal monooxygenase activities			-number of rats not given
Trottier et al. (1980)	rat[ζ]- male	fenitrothion (tech.- 97%) in sodium taurocholate -doses: 2.5, 5.0, 10.0 & 20.0 -control animals received vehicle -30-d study	oral (gavage)	-	-	-moderate to severe signs of toxicity observed in animals receiving 20 mg.kg-BW^{-1}.d^{-1} (8 of 36 animals died) -dose-dependant decrease in BW and tissue esterase activity (more marked effect on brain AChE than both PChE and RBC AChE) -all esterase activities were back to normal within 1-2 wk	-	2.5	-number of rats not given
Durham et al. 1982	rat-Sprague-Dawley[ζ] -males and females [45]	fenitrothion (tech. - 97%) in ethanol:propylene glycol alone and with 1.5% (v/v) each of Atlox 3409F and Dowanol TPM -doses: 1.0, 5.0, 10.0 & 20.0 -vehicle-treated controls -30-d study	oral (gavage)	-	-	-treatment with fenitrothion and/or the formulation resulted in dose-dependant inhibition in RBC and brain AChE, plasma PChE and hepatic and renal CE at doses above 1.0 mg.kg-BW^{-1}.d^{-1} -recovery of plasma PChE was very rapid but brain ChE recovery took > 2 mo -neither Atlox nor Dowanol substantially changed the toxicity of fenitrothion	1.0	5.0	

II.4. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	Comments
Kadota and Miyamoto (1975)	Japanese quail [260 female; 260 male]	Sumithion (tech.-97.2%) in corn oil -0.1, 1.5, 5, 15 & 50 mg.kg-diet^{-1} -4-wk study	oral (diet)	-	-	-dose-related dec. in whole blood ChE activity was observed in females of the 5 mg.kg^{-1} group and both females and males dosed at 15 and 50 mg.kg-diet^{-1} -significant reduction in brain ChE (both males and females) at 50 mg.kg-diet^{-1} -females seemed more sensitive -brain ChE recovery was slightly slower (4 wk compared with 2 wk for blood ChE)	1.5	5	
Kadota et al. (1975b) or Sumitomo (1976)	hen [16]	Sumithion (tech.-97.2%) in 10% Tween 80 -doses: 16.7 & 33.4 -4-wk study	oral	-	-	-slight BW decrease and intoxication symptoms at 16.7 mg.kg-BW^{-1}.d^{-1} -marked BW dec. and intoxication symptoms at 33.4 mg.kg-BW.d^{-1} -symptoms disappeared in 1 wk at low dose and 2 wk at high dose			-method of oral administration not given

[α] No IBT involvement, to our knowledge.

[β] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[γ] The conclusions on these studies are those found in FAO/WHO (1970).

[δ] See Appendix II.6 for replacement studies.

[ε] Wistar strain rats.

[ζ] Charles River strain rats.

Appendix II.5. Summary of inhalation studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing)	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[R] in NRCC monographs	Conclusions	NOEL	Lowest Effect Level	Comments
Sumitomo (1973)	rat	fenitrothion (tech.- 97.2%) -fine mist containing 7, 15 & 62 mg.m^{-3} for 2 h a day for 5 wk	inhalation	-	NRCC (1975)[Y] (p. 79)	-plasma ChE inhibited at 15 mg.m^{-3} and RBC and brain ChE inhibited at 62 mg.m^{-3}	7 mg.m^{-3}	15 mg.m^{-3}	
	rat and mouse	fenitrothion - fine mist containing 15 & 62 mg.m^{-3} for 2 h a day for 5 wk	inhalation	-	"	rats-plasma and RBC ChE inhibited at 15 mg.m^{-3} and brain ChE at 62 mg.m^{3} -similar effects in mice			
WHO (1973)	human	fenitrothion-3 different formulations of water-dispersible powder (unspecified) sprayed indoors to leave 2 g-AI.m^{-2} on the wall -3 rounds of spraying lasted 6 5-d work wk -4th rd - 8 wk	inhalation	-	NRCC (1975) (p. 79)	-slight to moderate depression of ChE in spraymen -total of 2000 man-days of spraying (only 1 complaint of headache) -no complaints from 20 000 inhabitants			

Appendix II.5. (Cont'd)

REFERENCE	Animal [number]	Compound (and dosing)	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[β] in NRCC monographs	Conclusions			Comments
							NOEL	Lowest Effect Level	
Vandekar (1965)	human [10 spray-men, 200 vil-lagers]	fenitrothion in water-dispersable powder (5% AI) -houses in S. Nigerian village sprayed to leave ~ 2 g-AI.m^{-2} on the surface -spraying lasted 2 days	inhala-tion	Alternate for IBT No. F9993	NRCC (1975) (p. 129) NRCC (1977a) (p. 419)	-significant plasma ChE depression in spraymen the day after spraying -inhabitants of the sprayed houses showed no plasma ChE inhibition 1 wk after spraying and a negligible inhibition 3 wk after spraying (this was statistically significant in the 7-14 yr-old age group)			-no definition of the exposure or dosage received by spraymen or villagers -assume spraying was indoors but this is unclear -reports have proved only that fenitrothion is safe enough to warrant its being subjected to an extended field trial

II.5. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing)	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[R] in NRCC monographs	Conclusions	NOEL	Lowest Effect Level	Comments
UPDATE Breckenridge et al. 1982	rat (albino) [120 male; 120 female]	fenitrothion (tech.-97%) (11% v/v) in an emulsion containing 1.5% Atlox 3409F and 1.5% Dowanol TPM in distilled water -concentrations of 6.7, 20.0 and 60.0 mg/L of air for 2 h.d^{-1} for 30 d -air-exposed controls	inhalation (nose-only)	-	-	-dose-dependant inhibition of brain and RBC ChE and plasma PChE and renal and hepatic CE, although only significant at 20 mg.L^{-1} or above -all esterase activities back to normal in 30 d post-treatment	6.7 mg.L^{-1}		
Chevalier et al. (1982)	rat [groups of 5 males]	fenitrothion (tech.-95%) in corn oil	intra tracheal (i.t.) injection -doses: 0, 2, 20 & 200 mg.kg-BW^{-1} once -killed at 1, 3, 7, 21, 60 & 180 d after injection	-	-	-LD_{50} determined to be 300 mg.kg-BW^{-1} for i.t. injection -acute pulmonary lesions were observed and found to be dose-dependant -the lesions had disappeared at all but the 200 mg.kg-BW^{-1} dose level by 180 d			-number of test animals not clear

II.5. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing)	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions			Comments
							NOEL	Lowest Effect Level	
Bioresearch (1983) #81405	rat (albino) [50 male; 50 female]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (24%) and Triton X114 (3%) in distilled water (59%) -doses: 0.603, 0.757, 1.473 and 1.689 $mg.L^{-1}$ for 4 h -air-exposed controls -observed for 14 d	inhalation (chamber)	-	-	-dose-related mortality for each sex (occurred within 9 d) -LC_{50} (males) reported to be 1.50 $mg.L^{-1}$ (95% CI 1.22-1.84) -LC_{50} (females) estimated to be >1.689 $mg.L^{-1}$ (highest dose tested) -salivation, ataxia, wetting of fur observed in all but low-dose animals -respiratory distress and discharge from nares also frequently observed -corneal opacities observed in most males (dose-related) at all dose levels, in females (5/10) at 2 highest doses -treatment-related vascular and inflammatory changes observed in animals that died		0.603 $mg.L^{-1}$	

II.5. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing)	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions	NOEL	Lowest Effect Level	Comments
Bioresearch (1983) (cont'd) #81374	rat (albino) [50 male; 50 female]	-fenitrothion tech. (14% w/w) with Cyclosol 63 (24%) and Triton X100 (3%) in distilled water (59%) -doses: 0.042, 0.865, 0.964 and 1.445 $mg.L^{-1}$ for 4 h -air-exposed controls -observed for 14 d	inhala-tion (chamber)	-	-	-dose-related mortality for each sex (occurred within 8 d) -LC_{50} (males) reported to be 1.15 $mg.L^{-1}$ (95% CI 0.93-1.43) -LC_{50} (females) estimated to be >1.445 $mg.L^{-1}$ (highest dose tested) -salivation and wetting of fur seen in almost all animals -respiratory distress seen occasionally in all exposure groups except low-dose group -slight BW loss in low-dose group and marked at higher doses -corneal opacities observed in 2-6 males at 3 highest dose levels, in 1 female at highest dose level -treatment-related atelectasis and neutrophil infiltration of alveolar tissue seen in 7/20 animals at highest dose level and in 1/20 in control		0.042 $mg.L^{-1}$	

II.5. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing)	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions			Comments
							NOEL	Lowest Effect Level	
Bioresearch (1983) (cont'd) #81404	rat (albino) [30 male; 30 female]	-fenitrothion tech. (14% w/w) with Triton X114 (14%) in distilled water (72%) -doses: 0.875 and 0.891 $mg.L^{-1}$ for 4 h -air-exposed controls -observed for 14 d	inhalation (chamber)	-	-	-dose-related mortality for males -all mortality occurred within 7 d -low mortality precluded the calculation of LC_{50}; estimated as = 0.891 $mg.L^{-1}$ (males) and > 0.891 $mg.L^{-1}$ (females) -salivation, lethargy, tremors and wetting of fur, particularly in males and in the high dose group -respiratory distress common in high dose group -dose-related decrease in lung weights in males increase in females -significant decrease in BW in high dose males but most had recovered by the end of the study -corneal opacities occurred in 8 males and 1 female at the high dose and 9 males at the low dose -= 50% of high-dose males showed signs of focal histiocytosis, broncho-pneumonia and necrotizing bronchitis		0.875 $mg.L^{-1}$	

II.5. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing)	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions			Comments
							NOEL	Lowest Effect Level	
Bioresearch (1983) (cont'd) #81375	rat (albino) [30 male; 30 female]	-fenitrothion tech. (14% w/w) with Triton X100 (14%) in distilled water (72%) doses: 0.830 and 0.976 $mg.L^{-1}$ for 4 h -air-exposed controls -observed for 14 d	inhalation (chamber)	-	-	-low mortality precluded any calculation of LC_{50}s; estimated as = 0.830 $mg.L^{-1}$ for both sexes -mortality occurred within 6 d -salivation, lethargy, ataxia and wetting of fur observed in most animals -body tremors, discharge from eyes or nares and respiratory distress frequently observed -marked BW losses in exposed groups -corneal opacities observed in 7 males and 2 females in low dose group and in 3 males and 1 female in high dose group -treatment-related bronchopneumonia noted in 7/20 animals in low dose group and focal histiocytosis in 4/20 animals in low dose group and 1/20 in high dose group		0.830 $mg.L^{-1}$	-nominal chamber concentration was higher for low dose group (this may explain higher number of corneal opacities and other effects observed in low-dose group)

[α] No IBT involvement, to our knowledge.

[β] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[γ] The study was reported incorrectly in NRCC (1975).

[δ] Bioresearch studies were received by the authors after Associate Committee review.

Appendix II.6. Summary of chronic dietary studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[R] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	Comments
Sumitomo (1972a)	rat (6-wk-old)	fenitrothion -doses: 10, 30 & 150 mg.kg-diet^{-1} -6-mo study	oral (diet)	-	NRCC (1975) (p. 78)	-depressed plasma ChE (45%) at 10 mg.kg-diet^{-1} (but no more ill-effects at conc. as high as 150 mg.kg-diet^{-1}) -plasma, RBC and brain ChE showed a dose-related decrease	-	10 mg.kg-diet^{-1}	
Klimmer (1961)	rat (male)	fenitrothion -doses: 10 & 11 -6-mo study	oral (gavage)	-	NRCC (1975)[γ] (p. 128)	-temporary deterioration of general condition and BW loss in 1st weeks -no effects seen in hematology, urinalysis or gross or micropathology			
Ueda and Nishimura (1966)	rat (male)	fenitrothion -doses: 0, 25, 100 & 400 mg.kg-diet^{-1} -16-mo study	oral (diet)	-	NRCC (1975)[γ] (p. 128)	-lethal dose - 400 mg.kg-diet^{-1} -100 mg.kg-diet^{-1} - slight inhibition of brain ChE & moderate inhibition of RBC and plasma ChE	25 mg.kg-diet^{-1}	100 mg.kg-diet^{-1}	
Sumitomo (1975a)	rat	Sumithion (97% pure, considered as 100% for calculations) -doses: 0, 2.5, 5 & 10 mg.kg-diet^{-1} -23-mo study	oral (diet)	-	NRCC (1975) (p. 78)	-plasma ChE showed a slight depression at 5 mg.kg-diet^{-1} and both plasma and RBC ChE at 10 mg.kg-diet^{-1} -brain ChE not effected	2.5 mg.kg-diet^{-1}	5 mg.kg-diet^{-1}	

II.6. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[R] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	Comments
Sumitomo (1975b)	rat (weanlings from Sumithion treated parents at 10, 30 and 150 mg.kg-diet^{-1})	Sumithion -doses: 0, 10, 30 & 100 mg.kg-diet^{-1} -26-mo study	oral (diet)	-	NRCC (1975) (p. 78)	-trend towards decreased body weight in males at 100 mg.kg-diet^{-1} -inhibition of plasma, RBC and brain ChE is dose-related and evident at 10 mg.kg-diet^{-1} (females more susceptible) -at 100 mg.kg-diet^{-1} - 6/10 treated females compared to 1/10 controls had slight to marked mammary cystic glandular dilation	-	10 mg.kg-diet^{-1}	
Sumitomo (1975c) or Burtner et al. (1974)	beagle dog	fenitrothion -12-mo study	oral (diet)	INVALID (IBT No. C1667)	NRCC (1975) (p. 79) NRCC (1977a) (p. 471)				
Sumitomo (1975c)	beagle dog [24 female; 24 male]	Sumithion (tech.-97%) -doses: 0, 30, 100 & 200 mg.kg-diet^{-1} -24-mo study	oral (diet)	Valid (IBT No. 651-09998) -also acts as an alternate for IBT Nos. C1667 and C9997	NRCC (1975) (p. 79)	-plasma ChE inhibited at 30 mg.kg-diet^{-1}, RBC and brain ChE inhibited at 100 and 200 mg.kg-diet^{-1} respectively -hematology, blood chemistry, ChE, urinalysis, gross pathology and histology unaffected	-	30 mg.kg-diet^{-1}	-appears as if same test material may have been used in 90-d and 12-mo studies (see Sumitomo 1975c)

II.6. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions		Comments
						NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	
UPDATE Kadota et al. (1975a)	rat[δ]	Sumithion (tech.- 97%) at 10, 30 & 150 mg.kg-diet^{-1}, Sumioxon (99%) at 5, 15 & 50 mg.kg-diet^{-1} and p-nitro-m-cresol (99.5%) at 150, 500 & 1500 mg.kg-diet^{-1} -6-mo study	oral (diet)	-	NRCC (1977a) (p. 471)	-no signs of toxicity -only dec. weight gain in Sumithion group (150 mg.kg-diet^{-1}), recovered by 2 wks -no significant effects in hematology, urinalysis, clinical biochem. except ChE -plasma, RBC and brain ChE of rats given Sumithion and Sumioxon showed a dose-related dec. -female plasma and brain ChE more susceptible than male		-vehicle not specified -dosage determined by recorded food consumption on a weekly basis -2nd part of study not included here because 50% of animals died of pneumonia
Ecobichon et al. (1980)	rat[δ] (weanling male)	fenitrothion (tech.- 97%) in peanut oil -doses: 0.5, 1.0, 5.0 & 10.0 -12-mo study	oral (gavage)	-		-dose-dependant inhibition of esterases -reductions in hepatic CE, brain and RBC AChE seen within 1st mo and then remained constant, levels of PChE, hepatic CE and RBC AChE back to normal 1 mo after treatment had ended, brain ChE normal 2 mo after		

II.6. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1}.d^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1}.d^{-1})	Lowest Effect Level (mg.kg-BW^{-1}.d^{-1})	Comments
IBT (1978)	monkeys [56]	Sumithion (tech.-97.3%) in corn oil -doses: 0, 0.1, 0.5 & 2.0 -control received vehicle -24-mo study	oral (gavage)	Valid (IBT No. 621-07168)	-	-significant inhibition in RBC and plasma ChE in both sexes, RBC ChE recovered by 24th mo	0.5	2.0	-wide fluctuations in cholinesterase activity levels during the administration period -photographs of motor-end plates in eye and foot muscle specimens were unclear -could not determine food consumption -gross tissue changes observed in lungs were considered those of intercurrent diseases -fur loss attributed to vitamin C deficiency
						-brain ChE not affected -minimal but consistent dose-related increase in the duration of insertional activity in the EMG for the 3 doses -increased number of segmented neutrophils in females at a dose of 2.0 mg.kg-BW^{-1}.d^{-1} after 2 mo -common effects on lungs observed at necropsy - yellow areas on lobes, adhesions or consolidation -fur loss noticed on many animals at ≈ 21 mo	2.0	-	

[α] No IBT involvement, to our knowledge.
[β] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.
[γ] The conclusions on these studies are those found in FAO/WHO (1970).
[δ] Wistar strain rats.

Appendix II.7. Summary of neurotoxicology studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comment
Sumitomo (1972d)	hen	fenitrothion -dose: up to 500 -5-wk study	oral	INVALID (IBT No. 8580-09445)	NRCC (1975) (p. 81)				-
Carshalton (1962) (Report No. OMS 43-S5660)	hens [3]	fenitrothion-single dose of 400 -protected with atropine and pralidoxime -observed for 28 d	oral	Alternate for IBT No. 8580-09445	NRCC (1975)[γ] (p. 126)	-no symptoms of paralysis observed -histopathologic examination of spinal cord and sciatic nerves revealed a few scattered degenerated fibres in the spinal cord of 1 hen			-
Kimmerle (1962) (Report No. S5660)	hen [10]	fenitrothion -7 hens given a dose of 250 and 3 given 500 -protected with atropine and pralidoxime -observed for 6 wk	oral	Alternate for IBT No. 8580-09445	NRCC (1975)[γ] (p. 126)	-2/3 in 500 mg.kg-BW^{-1} gp. died within 1-2 d -8 survivors showed no signs of paralysis			-

II.7. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions			Comments
							NOEL (mg.kg-BW^{-1})	Lowest Effect level (mg.kg-BW^{-1})	
UPDATE Kadota et al. (1975b) or Sumitomo (1976)	hen	Sumithion (tech - 97.2%) and Sumioxon 1. Preliminary study to calculate LD_{50} -Sumithion in 10% Tween 80 at single doses of 250, 500 & 1000 -Sumioxon in 10% Tween 80 at single doses of 10, 25, 50 & 100	oral (gavage)	Replacement for IBT No. 8580-09445	-	-calculated LD_{50} for Sumithion as 500 (384-650) mg.kg-BW^{-1} -LD_{50} for Sumioxon calculated as 35 (21-57) mg.kg-BW^{-1}			
	[16]	2. Delayed neurotoxicity -administered Sumithion (in Sorpol 355 and water) at a dose of 500 twice in a 3-wk interval -hens protected with atropine & 2-PAM -TOCP in 10% Tween 80 was used as a positive control	oral			-5/16 Sumithion treated hens died during 1st 24-48 h -toxic symptoms (motor ataxia, dec. spontaneous motor activity, irregular resp.) appeared early and then disappeared after 5-7 d, reappeared after 2nd dose -slight BW decrease in treated hens -no paralysis in legs -histopathological findings of sciatic nerves treated with Sumithion were normal -TOCP treated hens all suffered delayed neurotoxic effects -in a subacute study (see Kadota et al. (1975b) in AII.4), no paralysis in legs or abnormalities in sciatic nerves or spinal cord were observed			-TOCP, the positive control, was given in the vehicle Tween 80 and the test material was given in Sorpol 355 and water -method of administration not specified

II.7. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect level (mg.kg-BW^{-1})	Comments
Sumitomo (1977)	hen [16]	Sumithion (tech - 96.8%) in 10% Tween 80 given at a dose of 500 twice in a 3-wk interval -hens protected with atropine and 2-PAM -TOCP was used as the positive control -control hens given 10% Tween 80	oral	Replacement for IBT No. 8580-09445	-	-after 1st dose of Sumithion - 3/16 hens died after 5-7 d -10 of remaining 13 had positive paralytic symptoms[b] by 5th day which disappeared 5-9 d post-treatment -after 2nd dose - 3/13 hens died after 2-8 d -4 of remaining 10 had positive paralytic symptoms by 4th day which had disappeared 4-7 d post-treatment -no paralysis in legs observed after disappearance of toxic symptoms -slight dec. in BW in treated birds -no effects on sciatic nerves, spinal cord and brain -TOCP treated hens all suffered delayed neurotoxic effects			-method of oral administration not specified

II.7. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[β] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect level (mg.kg-BW^{-1})	Comments
Lehotzky and Ungvary (1976)		fenitrothion (tech - 95%)		-	-				-many results were unclear -method of oral administration often not given
	1. rat [40 males] [10 males] -20 controls	-single dose of 100 mg.kg^{-1}	oral			1. testing condition avoidance reflex -in rats at 100 mg.kg^{-1}: - number of positive conditioned responses dropped to 54% (controls 95%) within 2 h -extinction response slowed down in both test groups -whole blood ChE activity was inhibited (70%) during observation period (at 10 mg.kg-diet^{-1})			
		-10 mg.kg-diet^{-1}.d^{-1} for 30 d	oral						
	2. rabbits [18]	-10 mg.kg^{-1}.d^{-1} for 8 wk or 25 mg.kg^{-1}.d^{-1} for 4 wk	oral			2. conduction velocity of the sciatic nerve dec. at both doses -no signs of intoxication at lower dose although whole blood ChE inhibition was ≈ 50% -signs of poisoning at 25 mg.kg^{-1} -in rabbits treated with 10 mg.kg^{-1}, histopathological findings showed destruction of myelinated fibres of the sciatic nerve			

[α] No IBT involvement, to our knowledge.

[β] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[γ] The conclusions on these studies are those found in FAO/WHO (1970).

[δ] Loss of leg coordination and loss of balance.

Appendix II.8. Summary of reproductive and teratogenic studies on fenitrothion.

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Hazelton Lab. (1974)	rat	Sumithion (tech - 97%) -0, 10, 30 & 150 mg.kg-diet^{-1} through weaning of 1st gen. and then 0, 10, 30 & 100 mg.kg-diet^{-1} -3 generation study	oral (diet)	-	NRCC (1975) (p. 81)	-all parameters normal at 10 mg.kg-diet^{-1} -100 mg.kg-diet^{-1} was the effect level on reproduction data including the number and weight of weanlings	10 mg.kg-diet^{-1}	100 mg. kg-diet^{-1}	
IBT (1971j)	rabbit	Sumithion (tech - 97.1%) -doses: 0.3 & 1.0 -study from gestation days 6 through 18 and sacrificed on day 29	oral (capsule)	Valid (IBT No. J9996)	NRCC (1975) (p. 81)	-no teratogenic effects	1.0	-	-test material not confirmed -no raw information on parental age, strain and origin of animals -progeny data of control group missing
Fletcher et al. (1974a)	bobwhite quail	Sumithion in corn oil -doses: 3.0 & 10.0 mg.kg-diet^{-1} -positive control fed dieldrin at 3.0 mg.kg-diet^{-1} -study began 13 wk before laying and continued until hatching -chicks observed for 14 d	oral (diet)	Valid (IBT No. 651-04052)	NRCC (1975)[γ] but not evaluated (p. 81) NRCC (1977a) (p. 307)	-no effects on parental generation treated with Sumithion -no effects on eggs and hatchability or on viability and gross pathology of chicks -positive control group suffered increase in % of infertile eggs and decrease in viability of chicks	10.0 mg.kg-diet^{-1}	-	-test material unknown (assumed to be technical-97.1% purity) -age and origin of birds not given

II.8. (Cont'd).

REFERENCE	Animal [number]	Compound (and dosing in mg.kg-BW^{-1})	Route	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions	NOEL (mg.kg-BW^{-1})	Lowest Effect Level (mg.kg-BW^{-1})	Comments
Fletcher et al. (1974b)	mallard duck	Sumithion in corn oil -doses: 30 & 100 mg.kg-diet^{-1} -positive control fed dieldrin at 3.0 mg.kg-diet^{-1} -study began 8 wk before laying and continued until hatching -chicks observed for 14 d	oral (diet)	Valid (IBT No. 651-04052)	NRCC (1975)[γ] (not eval.)	-no effects on parental generation -no effects on eggs and hatchability or on viability and gross pathology of chicks	100 mg.kg-diet^{-1}		-test material unknown (as in Fletcher 1974a) -age and origin of birds not given -inaccurate transcription of raw data to final results - corrected
UPDATE Paul and Vadlamudi (1976)	white leghorn chick embryos	fenitrothion (100% EC) -dosed at 0.1, 0.5 and 1% (in 0.1 mL of H_2O) during the 4th - 12th day of incubation	inoculation into yolk space	-	-	-preliminary trials showed that conc. as low as 5% during days 4-12 were lethal -conc. of 0.1, 0.5 and 1% resulted in 40, 35 and 30% hatch respectively -conc. as low as 0.1% produced malformations (i.e. curled toe), leg weakness and abnormal gait -treatments given early in the incubation period were more toxic (i.e. hatchability rate, mortality, BW)	-	0.1% in 0.1 mL of H_2O (1×10^4 µg)	-purity of test material not given

[a] No IBT involvement, to our knowledge.

[δ] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[γ] The study was evaluated in this document.

Appendix II.9. Summary of mutagenic studies on fenitrothion.

REFERENCE	Type of Test	Species	Compound (and dosing in mg.kg-diet^{-1})	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions	Comments
Benes et al. (1973)	DLT (3-generation)	rat	fenitrothion (96%) -doses: 10, 40 & 80	-	NRCC (1975) (p. 81)	-no mutagenic effects observed under the explicit test conditions	
Miyamoto et al. (1976)	DLT		Sumithion (tech) in corn oil	-	NRCC (1977a) (p. 490)		
		rat (male)	-2, 7 & 20 mg.kg-BW^{-1} orally for 5 d			rats - no increased incidence of dominant lethal effects although sporadic increases were observed (not stat. significant or dose-dependant)	
		mouse (male)	-20, 200 mg.kg-BW^{-1} orally for 5 d			mice-fenitro. had no effects on numbers of corpora lutea, implantation sites, live and dead embryos -no significant increase in dominant lethal effects	
Suzuki and Miyamoto (1976)	host-mediated assays	mouse & S.t.[Y] G46	fenitrothion at 100 & 200 mg.kg-BW^{-1} orally or intramuscularly	-	NRCC (1977a) (p. 490)	-no increased mutation frequency	-DMSO used as the vehicle in controls
Suzuki and Miyamoto (1976)	Ames Test	S.t.[Y] TA1535, TAT537, TA1538	fenitrothion & metabolites dissolved in DMSO -dosed at 1, 10, 100 & 1000 µg/plate	-	NRCC (1977a) (p. 483)	-fenitrothion showed no mutagenic potential -negative in Ames test for 1) reverse mutation 2) DNA damage capacity	

II.9. (Cont'd).

REFERENCE	Type of Test	Species	Compound (and dosing in mg.kg-diet^{-1})	IBT STATUS ("valid"; invalid; replacement; alternate; or -[a])	Presence[a] in NRCC monographs	Conclusions	Comments
Miyamoto and Suzuki (1977)		S.t.[Y] TA100 & TA98 S.t. TA100 and TA98 with and without liver S9 fractions of female rats pretreated with a microsomal enzyme inducer	fenitrothion and metabolites dissolved in DMSO, 1, 10, 100 and 1000 ug/plate	-	NRCC (1977a) (p. 483)	-suggests that none of the degradation products are mutagenic although m-hydroxymethyl fenitrothion gave slighter larger numbers of revertant colonies of TA100	
Suzuki et al. (1975)		Escherichia coli K12 and coli-phage[λ]	fenitrothion	-	NRCC (1975) (p. 81)	-fenitrothion showed little mutagenic and radiomimetic potential	
Benes and Sram (1969)	Muller-5 genetic test	Drosophila melanogaster	fenitrothion	-	NRCC (1975) (p. 81)	-no evidence of recessive lethality in the X-chromosome under explicit test conditions	
UPDATE Benes et al. (1975)	DLT (4 generation) and cytogenetic analysis of chromosome aberrations	rat	fenitrothion (tech. - 96%) at doses of 0, 10, 40 & 80	-	-	-no increase in the frequency of dominant lethals -no increased number of chromosome breaks or exchanges	-number of test animals not given -ignored rats where the fetuses were resorbed + underestimated impact?

II.9. (Cont'd).

REFERENCE	Type of Test	Species	Compound (and dosing in mg.kg-diet^{-1})	IBT STATUS ("valid"; invalid; replacement; alternate; or -[α])	Presence[R] in NRCC monographs	Conclusions	Comments
Njagi et al. (1980)	-tested for induction of sex-linked recessive lethals	Drosophila melanogaster	fenitrothion in demineralized water and used in the BASC-technique at 0.001%	-	-	-no recessive lethals induced	
Gopalan and Njagi (1979) (Abstract only)	-examined chromosome aberrations	Vicia faba	fenitrothion	-	-	-fenitrothion induced acute mitostatic effects, formation of pycnotic nuclei and premature chromosome condensation in Vicia faba	Abstract only
Njagi and Gopalan (1981)	-examined chromosome aberrations	Vicia faba	fenitrothion (50% AI; 100 mg.kg^{-1} for 120 min)	-	-	-mitotic inhibition, pycnosis and premature chromsome condensation (same as above)	-does not give control -all 12 chemicals tested caused the same results as did fenitrothion -claim effects were dose/rate dependent but give no data

[α] No IBT involvement, to our knowledge.

[R] Studies that were examined in NRCC (1975) or presented in NRCC (1977a) are taken "verbatim" from those documents and were not reexamined.

[Y] Salmonella typhimurium.

APPENDIX III.O

Trade Memorandum of Guidelines for Pesticide Toxicology Data Requirements

Agriculture Canada

FOOD PRODUCTION AND INSPECTION BRANCH / DIRECTION GÉNÉRALE, PRODUCTION ET INSPECTION DES ALIMENTS	DATE October 30, 1981	R-1-211
	PESTICIDES DIVISION	

MEMORANDUM TO REGISTRANTS

Re: Guidelines for Pesticide Toxicology Data Requirements

The purpose of this memorandum is to request the comments of registrants and other interested groups and agencies on draft guidelines for pesticide toxicology data.

The need for definitive toxicology data guidelines for pesticide registration has been repeatedly expressed in various quarters, including provincial regulatory agencies and pesticide manufacturers. Over the past several months the Pesticides Division of Agriculture Canada has worked cooperatively with colleagues in the Health Protection Branch of Health and Welfare Canada to develop draft guidelines which reflect the types of tests generally needed in delineating the toxicity of a pesticide and its potential hazard to humans.

The attached data guideline has benefited from a constructive review by various provincial health officials and representatives of the pesticide manufacturing industry.

We believe that these guidelines represent substantive progress in clearly and visibly identifying, for the benefit of the regulatory community, pesticide manufacturers and the public, one of the major data areas required to support pesticide registration. However, we appreciate that our consultation on this matter, while extensive, may not be all encompassing. For this reason we are providing, via this memorandum, an opportunity for the broadest comment from all segments of the pesticide manufacturing industry as well as other groups or agencies who may have an interest in this matter.

Please submit your comments by December 15, 1981

S.W. Ormrod
Director
Pesticides Division

Distribution: KP, PP, PW, PX, all registrants.

HEALTH PROTECTION BRANCH

GUIDELINES FOR PESTICIDE TOXICOLOGY DATA REQUIREMENTS

1. Summary

The Health Protection Branch's mandate with respect to the safety of pesticides involves the assessment of health hazards, from residues in food and from occupational and bystander exposure, resulting from proposed new uses and existing uses of pesticides.

In the area of pesticide residues in food, the Health Protection Branch administers the Food and Drug Regulations. Any pesticide which is used on food or may contaminate food in any way must be evaluated by the Food Directorate to determine the nature, level and toxicity of such residues and to determine the residue limits which may be necessary under the Food and Drug Regulations.

In the case of occupational or bystander health hazards, the Health Protection Branch advises other agencies, particularly Agriculture Canada who administer the Pest Control Products Act. Any pesticide which is sold or used in Canada must be evaluated by the Environmental Health Directorate to determine the possible hazards to people exposed occupationally or inadvertently (bystanders).

In order to evaluate new pesticides, new uses of existing pesticides and to re-evaluate presently used pesticides, extensive data are needed by both the Food Directorate and the Environmental Health Directorate. The attached guidelines for pesticide toxicology data are intended to assist applicants in selecting the type of toxicity tests which would be essential to the evaluations of pesticide hazards. It should be noted, however, that the Health Protection Branch considers that the applicant is responsible for proving the safety of any pesticide they wish to use or sell in Canada. The applicant is also responsible for discussing detailed data requirements for specific chemicals with Health Protection Branch officials.

These guidelines should not be construed as inflexible requirements but rather as an outline of the types of tests generally needed in delineating the toxicity of a chemical and potential hazards to humans. It is conceivable that some of the tests and species listed might be unwarranted for certain products, and the Health Protection Branch reserves the right to request additional toxicity studies if considered to be necessary.

It is not the intention in these guidelines to detail protocols for tests, and applicants should consult protocols developed and published by various agencies, including Health Protection Branch, Health and Welfare Canada, the Environmental Protection Agency in the U.S.A., the World Health Organization, the International Agency for Research on Cancer (IARC) and Organization for Economic Cooperation and Development (OECD).

2. Data Organization

Trade Memorandum T-1-212, dated September 8, 1980 issued by Agriculture Canada outlines the format for organizing all data in submissions together with the required distribution of copies. It should be noted that the Health Protection Branch requires data on all aspects outlined in Trade Memorandum T-1-212, except for efficacy data, although these guidelines relate only to toxicology data requirements.

3. Test Substance

Under most circumstances, the test substance will be the technical grade of the active ingredient that is produced during the normal manufacturing process. Under certain circumstances, it may be required that an analytically pure grade of the active ingredient, an inert ingredient of the formulation, a contaminant or impurity, a metabolite or degradation product, or any combination of these be tested. Some tests, as outlined below, must be conducted on the formulation.

4. Acute Toxicity Studies

Most of these studies define the dosage and range of a single or multiple administration of the pesticide within a 24-hour period or less which is lethal. The data from these studies, as well as the results from dermal irritation, eye irritation and dermal sensitization studies are used to identify the relative toxicity of the product for classification and for label precautionary statements. Preliminary information may also be obtained on the specific toxic effects and the mode of action. Whenever appropriate, no-effect levels (NOEL) should also be determined because this information is useful in estimating the potential hazard from acute exposures.

5. Short Term Studies

These studies delineate the toxic potential of the pesticide through repeated administration for less than one sixth of the lifespan of these test species. The data obtained are useful in elucidating such problems as possible cumulative action, variation in species sensitivity and in identifying specific

organ effects. They also provide guidance for the selection of dosages for chronic studies.

Since the 90-day oral study has been widely used, it is suggested that this be done for purposes of comparison only with the technical material. However, to evaluate the potential hazard of a product to workers or bystanders, subchronic studies should be conducted using the dermal and/or inhalation route of exposure with both the technical and formulated product. The duration of these studies and the appropriate route of exposure should be determined after the results from the pharmacokinetic studies are evaluated. Also the use pattern and physical properties of the product will assist in determining the appropriate studies.

6. Long Term Studies

These studies provide information on the maximum dosage level which produced no discernable injury to animals when administered over the major portion of the life span of the test animals and reveal effects which are not predictable from short term toxicity studies.

Unless data from the other studies indicate otherwise, the long term studies should be conducted using normal technical material administered by the route usually used for the specific test.

SPECIAL STUDIES

(i) Pharmacokinetic Studies:

A good understanding of the pharmacokinetics will enable more judicious selection of appropriate routes of administration, dose levels and actual tests which should be done on a product and assist on the evaluation of potential human health hazards.

(ii) Mutagenicity Tests:

These tests will be used primarily to screen for the carcinogenic potential of the product. The limitations of these tests are realized, but it is felt that they might provide useful information which could be used along with the results from the whole animal experiments to give some preliminary indication of carcinogenic potential.

(iii) Studies of Breakdown Products:

Toxicity studies on metabolic and environmental breakdown products may be necessary to evaluate the potential hazards of human exposure to such chemicals in both food and in treated areas which must be entered by workers and bystanders.

(iv) Teratogenicity Studies:

These studies should provide data on the potential of pesticides to produce or alter the incidence of congenital malformations.

(v) Reproduction Studies:

These studies provide information on the potential effects the pesticides might have on the reproductive capacities of the parental generation from mating through lactation and on the offspring from conception through lactation and mating. The study should be conducted on two litters from each of two generations.

(vi) Exposure Studies:

These studies should be conducted only after there is reasonable assuredness that the applicator will not be placed at undue risk and could coincide with efficacy field trials. These studies will be used to determine the magnitude of the margin of safety under use conditions and appropriate protocols shall be determine after consultation.

GUIDELINES FOR PESTICIDE TOXICOLOGY DATA

	Technical	Formulation	Suggested Species	Sex	Comments
Acute (including NOEL where applicable)	Oral LD_{50}	Oral LD_{50}	Rat and Dog	M & F	
	Dermal LD_{50}	Dermal LD_{50}	Rabbit or Rat	M & F	
	Inhalation LC_{50}	Inhalation LC_{50}	Rat	M & F	
	Primary Dermal Irritation	Primary Dermal Irritation	Rabbit	M or F	
	Primary Eye Irritation	Primary Eye Irritation	Rabbit	M or F	If required
	Dermal Sensitization	Dermal Sensitization	Guinea Pig or Rabbit	M	
	Delayed Neurotoxicity		Chicken	F	for CHE inhibitors
	Antidotes				

GUIDELINES FOR PESTICIDE TOXICOLOGY DATA

	Technical	Formulation	Suggested Species	Sex	Comments
Short Term	90-day Oral with Recovery Studies		Rat and Dog	M & F	
	12-month Oral		Dog	M & F	May be combined with 90 day dog study
	90-day Dermal with Recovery Studies	21-day Dermal	Rabbit or rat	M & F	
	90-day Inhalation with Recovery Studies	21-day Inhalation	Rat	M & F	
	Delayed Neuro-toxicity if Positive in Acute Tests		Chicken or Mammal	F M & F	

GUIDELINES FOR PESTICIDE TOXICOLOGY DATA

	Technical	Suggested Species	Sex	Comments
Long Term	Chronic Feeding	Rat	M & F	Studies may be combined
	Oncogenicity	Rat	M & F	
	Oncogenicity	Mouse	M & F	

GUIDELINES FOR PESTICIDE TOXICOLOGY DATA

	Technical	Formulation	Suggested Species/Sex	Comments
Special Studies*	Pharmacokinetic Studies - absorption, distribution excretion and metabolism		Appropriate to Route Being Studied	Details to be discussed
	In vitro Mutagenicity a) Point Mutation - microbial - mammalian			Positive results may indicate in vivo studies
	b) Chromosomal Aberrations			
	c) DNA Repair			
	Teratogenicity		2 of: Rat Mouse Hamster Rabbit	
	Multi-generation Reproduction		One of species used for teratogenicity study, preferably Rat	2 generation, 4 litter study as minimum
		Exposure Studies		Done at the time of efficacy trials

* Sub-acute and chronic toxicity studies on environmental breakdown products may be required depending on quantities and significance (e.g. significant plant metabolites which do not occur in animal metabolism studies).

APPENDIX IV.0

Validation Summary of Fenitrothion

Supplied by Health and Welfare Canada

VALIDATION SUMMARY

DATE: August 3, 1982

RATING: No longer of concern with respect to IBT

COMPOUND: FENITROTHION (Folithion, Novathion, Sumithion)

IBT STUDY NO.	STUDY TYPE	SPECIES	AUDIT RESULTS	REPLACEMENTS/ALTERNATES
8580-09445	42-day delayed neurotoxicity	chicken	invalid	Replacement submitted.
601-04051	eye irritation	rabbit	invaiid	Replacement submitted.
C 9997	90-day oral	dog	invalid	Alternate available.
C 1667	12-month oral cholinesterase	dog	invalid	Alternate available.
F 9999	3-month oral cholinesterase	human	invalid	Alternate available.
J 9992	oral LD_{50}	duck	invalid	Alternate available.
J 9995	teratology (pilot)	rabbit	invalid	Alternate available.
621-07168	2-year oral	monkey	valid	
651-09998	2-year oral	dog	valid	
J 9996	teratology	rabbit	valid	
651-04052	1-generation reproduction	quail	valid	
651-04052	1-generation reproduction	duck	valid	

VALIDATION SUMMARY

DATE: August 3, 1982

RATING: No longer of concern with respect to IBT

COMPOUND: FENITROTHION (Folithion, Novathion, Sumithion) cont'd.

IBT STUDY NO.	STUDY TYPE	SPECIES	AUDIT RESULTS	REPLACEMENTS/ALTERNATES
J 100	oral LD_{50}	dog	valid	
J 101	oral LD_{50}	dog	valid	
J 102	oral LD_{50}	duck	valid	
J 103	oral LD_{50}	pheasant	valid	
J 104	oral LD_{50}	duck	valid	
J 105	oral LD_{50}	pheasant	valid	
J 9993	oral LD_{50}	pheasant	valid	
J 9994	oral LD_{50}	dog	valid	

Note: An adequate non-IBT data base is available for Fenitrothion (see Publication No: NRCC 15389).

STATUS OF REPLACEMENT/ALTERNATE STUDIES FOR INVALID IBT STUDIES
WITH FENITROTHION (SUMITHION)

IBT STUDY NO.	STUDY TYPE	SPECIES	ALTERNATE/REPLACEMENT STUDY (IES)	COMMENTS
8580-09445	Neurotoxicity	Chicken	(a) Sumitomo Chemical Co., Ltd. (Osaka, Japan); Report No. HT-60-0026 (August 1979) (b) Sumitomo Chemical Co., Ltd. (Osaka, Japan); Report No. HT-70-0200 (February 1977) (c) Kadota, T., Okuno, Y. and Miyamoto, J. in Botyu-Kagaku (Sc. Pest. Contr.) 40, 49-53, 1975 (d) Toxicology Research Unit (Carshalton) Report No. OMS 43-S5660 (1962) (e) Toxikologisches Und Gewerbe-hygienisches Laboratorium (Germany) Report No. S5660 (1962)	

Titles: IBT No. 8580-09445: "Neurotoxicity Study with Sumithion in Chickens", November 2, 1976
Replacement/Alternate: (a) "Acute Oral Toxicity and Delayed Neurotoxicity of Sumithion in Hens", Report No. HT-60-0026, Aug. 1976.
(b) "Delayed Neurotoxicity Study with Sumithion in Hens", Report No. HT-70-0200, Feb. 22, 1977.
(c) "Acute Oral and Delayed Neurotoxicity of 5 Organophosphorus Compounds, Salithion, Cyanox, Surecide, Sumithion and Sumioxon in Adult Hens" (published in Botyu-Kagaku, 40 49-53, 1975) - For summary, see WHO Techn. Rep. Ser. 1977.
(d) "Tests for Neurotoxic Effects in Hens", Mammalian Toxicity Report OMS 43-S5660 (1962) - For summary, see WHO Techn. Rep. Ser. 1969.
(e) Unpublished report on the Neurotoxic Effect of Fenitrothion on Hens - For summary, see WHO Techn. Rep. Ser. 1969.

IBT STUDY	STUDY TYPE	SPECIES	ALTERNATE/REPLACEMENT STUDY (IES)	COMMENTS
601-04051	Eye Irritation	Rabbit	(a) Sumitomo Chemical Co. Ltd. (Osaka, Japan) Report No. HT-10-0201 (March 1981) (b) Sumitomo Chemical Co. Ltd. (Osaka, Japan) Report No. (?) ST-I-3	
Titles: IBT No. 601-04051: "Eye Irritation Tests with Sumithion in Albino Rabbits", October 31, 1973 Replacement/Alternate: (a) "Primary Eye and Skin Irritation Tests of Sumithion Technical in Rabbits", Report No. HT-10-0201, March 31, 1981. (b) Report title not available (study reviewed by HPB- April 3, 1973).				
J 9992	Acute Oral	Duck	Replacement deemed unnecessary- See comments	A replacement/alternate study is not available with ducks per se. A host of studies with other avian species, including Japanese quail, Ringneck pheasant and chickens, are available. -See Kodota and Miyamota, Botyu-Kagaku (Sci. Pest. Control) 40, 54-58, 1975 (Summary available in WHO Tech. Rep. Ser. 1977).
Titles: IBT No. J9992: "Acute Oral Toxicity Study with Sumithion Technical in Mallard Ducks", August 17, 1971.				

IBT STUDY NO.	STUDY TYPE	SPECIES	ALTERNATE/REPLACEMENT STUDY (IES)	COMMENT
F 9999	Cholinesterase	Human	(a) Vandekar, M. In Bull. Wld. Hlth. Org. 33, 107-15, 1965 (b) Wilford et al. In WHO Working Paper 65/Tox/1 (1965) (c) Nosal and Hladka In Internat. Arch. Gewerbepath. 25, 28-38, 1968	These reports summarize field trial observations encompassing occupational and bystander exposure and effects on blood cholinesterase activities. Data summaries are available in WHO Techn. Rep. Ser. 1969. An additional human study (report title and/or source not specified) was reviewed by HPB September 25, 1968.

Titles: IBT No. F9999: "A Study on the Effects of Sumithion on Plasma and Erythrocyte Cholinesterase Activity in Human Subjects During Subacute Oral Administration", March 30, 1972.
Replacement/Alternate: (a) "Observations on the Toxicity of Carbaryl, Folithion and 3-Isopropylphenyl N-Methylcarbamate in a Village-Scale Trial in Southern Nigeria"
(b) "Toxicological Observations During Large Scale Field Trials of OMS-43 in Northern Nigeria"
(c) "Determination of the Exposure to Fenitrothion on the Basis of the Excretion of P-nitro-m-cresol by the Urine of the Persons Tested"

J 9995	Teratology (Pilot)	Rabbit	Industrial Bio-Test Laboratories, Inc. (Northbrook, Il) Report No. J-9996 (December 1971)	IBT No. J-9996, declared valid, is a suitable alternate.

Titles: IBT No. J9995: Report title not available.
Replacement/Alternate: "Teratogenic Study with Sumithion Technical in Albino Rabbits", IBT No. J-9996, December 15, 1971.

C-9997	Subchronic (90-Day) Oral	Dog	Industrial Bio-Test Laboratories, Inc. (Northbrook, Il) Report No. 651-09998 (October, 1973)	IBT No. 651-09998, declared valid, has been deemed to be an adequate alternate.

Titles: IBT No. C-9997: "90-Day Subacute Oral Toxicity Study with Sumithion Technical in Beagle Dogs, February 10, 1972.
Replacement/Alternate: "Two-Year Chronic Oral Toxicity Study with Sumithion Technical Grade in Beagle Dogs", IBT No. 651-09998, October 12, 1973.

IBT STUDY NO.	STUDY TYPE	SPECIES	ALTERNATE/REPLACEMENT STUDY (IES)	COMMENT
C 1667	1-Year Oral Cholinesterase	Dog	See comments.	The sponsor has agreed to conduct a replacement study (see correspondence A. Okumura, Sumitomo, to W.P. McKinley June 22, 1981). Pending receipt of the replacement data, IBT No. 651-09998 (see above) may serve as an alternate study.

Titles: IBT No. C1667: One-Year Chronic Oral Toxicity of Sumithion Technical on Cholinesterase Activity in Beagle Dogs, July 23, 1973.

REFERENCES

Altman, P.L. and Dittmer, D.S. 1974. Biology Data Book. 2nd Ed. Volume III. Fed. Am. Soc. Exp. Biol., Bethesda, Maryland.

Benes, V. and Sram, R.J. 1969. Mutagenic activity of some pesticides in Drosophila melanogaster. Indust. Med. 38(12): 50-52. As cited in NRCC (1975).

Benes, V., Sram, R.J. and Tuscany, R. 1973. Testing of mutagenicity of fenitrothione. Mutat. Res. 21(1): 23-24. (Abstract only) As cited in NRCC (1975).

Benes, V., Sram, R.J. and Tuscany, R. 1975. Fenitrothion. I. Study of mutagenic activity in rats. J. Hyg. Epidemiol. Microbiol. Immunol. 19(2): 163-172.

Bioresearch Laboratories Ltd. 1982a. Acute oral toxicity study in albino rats administered test article fenitrothion formulation (with: 1) Cyclosol 63 and Triton X114; 2) Cyclosol 63 and Triton X100; 3) Triton X114 and; 4) Triton X100). Project Nos. 50322, 50321, 50273, 50272. Report to Forest Protection Ltd., New Brunswick.

Bioresearch Laboratories Ltd. 1982b. Acute dermal toxicity study in albino rabbits administered test article fenitrothion formulation (with: 1) Cyclosol 63 and Triton X114; 2) Cyclosol 63 and Triton X100; 3) Triton X114 and; 4) Triton X100). Project Nos. 50328, 50327, 50285, 50284. Report to Forest Protection Ltd., New Brunswick.

Bioresearch Laboratories Ltd. 1982c. Primary dermal irritation study in albino rabbits administered test article fenitrothion formulation (with: 1) Cyclosol 63 and Triton X114; 2) Cyclosol 63 and Triton X100; 3) Triton X114 and; 4) Triton X100). Project Nos. 50326, 50325, 50281, 50280. Report to Forest Protection Ltd., New Brunswick.

Bioresearch Laboratories Ltd. 1982d. Primary eye irritation study in albino rabbits administered test article fenitrothion formulation (with: 1) Cyclosol 63 and Triton X114; 2) Cyclosol 63 and Triton X100; 3) Triton X114 and; 4) Triton X100). Project Nos. 50324, 50323, 50334, 50333. Report to Forest Protection Ltd., New Brunswick.

Bioresearch Laboratories Ltd. 1982e. Dermal sensitization study in albino guinea pigs administered test article fenitrothion formulation (with: 1) Cyclosol 63 and Triton X114; 2) Cyclosol 63 and Triton X100; 3) Triton X114 and; 4) Triton X100). Project Nos. 50330, 50329, 50277, 50276. Report to Forest Protection Ltd., New Brunswick.

Bioresearch Laboratories Ltd. 1983. The acute toxicity of inhaled fenitrothion (with: 1) Triton X114 and Cyclosol 63; 2) Triton X100 and Cyclosol 63; 3) Triton X114 and; 4) Triton X100) in the albino rat. Project Nos. 81405, 81374, 81404, 81375. Report to Forest Protection Ltd., New Brunswick.

Braid, P.E. and Nix, M. 1968. Potentiation of toxicity of Sumithion by phosphamidon in the rat. Can. J. Physiol. Pharmacol. 46: 145-149. As cited in FAO/WHO (1970).

Breckenridge, C., Pesant, M., Durham, H.D. and Ecobichon, D.J. 1982. A 30-day toxicity study of inhaled fenitrothion in the albino rat. Toxicol. Appl. Pharmacol. 62: 32-43.

Burtner, B.R., Kennedy, G.L. and Keplinger, M.L. 1974. Ninety-day subacute oral toxicity study, one-year oral cholinesterase activity study, and two-year chronic oral toxicity study with Sumithion technical in beagle dogs. Report by Industrial Biotest Laboratories Inc. to Sumitomo Chemical Co., Ltd., Japan. Same report as Sumitomo (1975c).

Carshalton. 1962. WHO insecticide evaluation and testing programme-Stage I. Test for neurotoxic effects in hens. Mammalian toxicity report OMS 43-S5660. Toxicology Research Unit, Carshalton. As cited in FAO/WHO (1970).

Carshalton. 1964. Mammalian toxicity - Summary. Toxicology Research Unit, Carshalton. OMS 43. As cited in FAO/WHO (1970).

Chevalier, G., Bastié-Sigeac, I. and Côté, M.G. 1982. Morphological assessment of fenitrothion pulmonary toxicity in the rat. Toxicol. Appl. Pharmacol. 63: 91-104.

Cooper. 1966. Toxicity of Sumithion. Report by Cooper Technical Bureau to Sumitomo Chemical Co., Ltd., Japan. As cited in FAO/WHO (1970).

Crabbe, R.S. and Reid, J.D. 1980. Results from two models for the long-distance drift and dry deposition of an insecticide cloud onto a forest. AMS, APCA Second Joint Conference on Applications of Air Pollution Meteorology, New Orleans. March 24-27, 1980.

Crabbe, R., Krzymien, M., Elias, L. and Davie, S. 1980. New Brunswick spray operations: measurement of atmospheric fenitrothion concentrations near the spray area. National Research Council Canada. Report No. LTR-UA-56.

Degraeve, N., Gilot-Delhalle, J., Moutschen, J., Moutschen-Dahmen, M., Colizzi, A., Chollet, M. and Houbrechts, N. 1980. Comparison of the mutagenic activity of organophosphorus insecticides in mouse and in the yeast Schizosaccharomyces pombe. Mutat. Res. 74(3): 201-202. (Abstract only)

Dubois, K.P. and Kinoshita, F. 1963. The acute toxicity of Bayer 41831 in combination with other anticholinesterase insecticides. Dept. of Pharmacology, University of Chicago. As cited in FAO/WHO (1970).

Dubois, K.P. and Puchala, E. 1960. The acute toxicity and anticholinesterase action of Bayer 41831. Unpublished report from the Dept. of Pharmacology, University of Chicago. As cited in FAO/WHO (1970).

Durham, H.D., Comeau, A.M., Cameron, P.H. and Ecobichon, D.J. 1982. Subacute toxicity in rats of orally administered fenitrothion alone and in a selected formulation. Toxicol. Appl. Pharmacol. 62: 455-464.

Ecobichon, D.J. 1983. Information supplied to the authors. McGill University, Montreal.

Ecobichon, D.J. and Zelt, D. 1979. The acute toxicity of fenitrothion in weanling rats and effects on tissue esterases and mono-oxygenases. Toxicology 13: 287-296.

Ecobichon, D.J., Ozere, R.L., Reid, E. and Crocker, J.F.S. 1977. Acute fenitrothion poisoning. Can. Med. Assoc. J. 116: 377-379.

Ecobichon, D.J., Comeau, A.M. and Cameron, P.H. 1980. Chronic toxicity of technical fenitrothion in male rats. Toxicol. Appl. Pharmacol. 56: 409-417.

EPA. 1983. Summary of the IBT Review Program, Office of Pesticide Programs. United States Environmental Protection Agency, Washington, D.C.

EPS. 1978. Environmental monitoring of the 1976 spruce budworm spray program in New Brunswick, Canada. Environmental Protection Service. Surveillance Report EPS-5-AR-78-3.

Eto, M. 1974. Organophosphorus pesticides: organic and biological chemistry. CRC Press, Inc., Cleveland, Ohio.

FAO/WHO. 1970. Toxicological studies. In 1969 Evaluations of some pesticide residues in food. Food and Agriculture Organization/World Health Organization.

Fletcher, D., Jenkins, D.H. and Keplinger, M.L. 1974a. Toxicity and reproduction study with Sumithion in bobwhite quails. Report by Industrial Bio-test Laboratories Inc. to Sumitomo Chemical Co., Ltd., Japan. IBT No. 651-04052.

Fletcher, D., Jenkins, D.H. and Keplinger, M.L. 1974b. Toxicity and reproduction study with Sumithion in mallard ducks. Report by Industrial Bio-test Laboratories Inc. to Sumitomo Chemical Co., Ltd., Japan. IBT No. 651-04052.

Fukami, Y. 1976. Ocular injuries to rats in experimental intoxication by an organophosphorus pesticide, fenitrothion. Rinsho Ganka 30(7): 841-848. (English abstract in Pest. Abstr. 76: 863.)

Fullerton, P.M. and Barnes, J.M. 1966. Peripheral neuropathy in rats produced by acrylamide. Br. J. Ind. Med. 23: 210-221.

Gaines, T.B. 1969. Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14: 515-34. As cited in FAO/WHO (1970).

Gopalan, H.N.B. and Njagi, G.D.E. 1979. Cytogenetic studies in Vicia faba with some insecticides, fungicides and herbicides. Environ. Mutag. 1(2): 141-142. (Abstract only)

Hartling, L. 1983. A preliminary report on the 1983 foliage protection program against the spruce budworm in New Brunswick. New Brunswick Dept. of Natural Resources. Reported to the Forest Pest Control Forum, Ottawa.

Hayes, W.J. 1975. Toxicology of pesticides. The Williams and Wilkins Co., Baltimore, Maryland.

Hayes, W.J. 1982. Pesticides studied in man. Williams and Wilkins, Baltimore, Maryland.

Hazelton Lab. 1974. Toxicology studies. Part III. Three-generation reproduction study in rats. Report to Sumitomo Chemical Co., Ltd., Japan.

Heath, R.G., Spann, J.W., Hill, E.F. and Kreitzer, J.F. 1972. Comparative dietary toxicities of pesticides to birds. U.S. Dept. Interior, Fish Wildl. Serv., Bur. Sport Fish. Wildl., Spec. Sci. Rep., Wildl. No. 152.

HWC. 1983. Information supplied to the authors. Health and Welfare Canada.

HWC. 1984. Information supplied to the authors. Health and Welfare Canada.

IBT. 1971a. Acute oral toxicity study of Sumioxon pure in beagle dogs. Industrial Bio-test Laboratories Inc. IBT No. J100. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971b. Acute oral toxicity study with p-nitro-meta-cresol in beagle dogs. Industrial Bio-test Laboratories Inc. IBT No. J101. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971c. Acute oral toxicity study with Sumioxon pure in mallard ducks. Industrial Bio-test Laboratories Inc. IBT No. J102. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971d. Acute oral toxicity study with Sumioxon pure in ringneck pheasants. Industrial Bio-test Laboratories Inc. IBT No. J103. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971e. Acute oral toxicity of p-nitro-meta-cresol in mallard ducks. Industrial Bio-test Laboratories Inc. IBT No. J104. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971f. Acute oral toxicity of p-nitro-meta-cresol in ringneck pheasants. Industrial Bio-test Laboratories Inc. IBT No. J105. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971g. Acute oral toxicity with Sumithion technical in mallard ducks. Industrial Bio-test Laboratories Inc. IBT No. J9992. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971h. Acute oral toxicity study of Sumithion technical crude in ringneck pheasants. Industrial Bio-test Laboratories Inc. IBT No. J9993. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971i. Acute oral toxicity study of Sumithion technical in beagle dogs. Industrial Bio-test Laboratories Inc. IBT No. J9994. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1971j. Toxicology studies. Part IV. Teratogenic study with Sumithion in albino rabbits. Industrial Bio-test Laboratories Inc. IBT No. J9996. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1972. Toxicology studies. Part II. A study of the effects of Sumithion on plasma and erythrocyte cholinesterase activity in human subjects during subacute oral administration. Industrial Bio-test Laboratories Inc. IBT No. F9999. Report to Sumitomo Chemical Co., Ltd., Japan.

IBT. 1978. Two-year chronic oral toxicity of Sumithion technical in cymologous monkeys. Industrial Bio-test Laboratories Inc. IBT No. 621-07168. Report to Sumitomo Chemical Co., Ltd., Japan.

ICRP. 1975. Report of the Task Group on Reference Man. International Commission on Radiological Protection No. 23. Pergamon Press, Oxford.

Johnson, J.C. Jr. and Bowman, M.C. 1972. Responses from cows fed diets containing fenthion or fenitrothion. J. Dairy Sci. 55: 777-782. As cited in NRCC (1975).

Kadota, T. and Miyamoto, J. 1975. Acute and subacute toxicity of fenitrothion in Japanese quails. Bochu-Kagaku 40(2): 54-58.

Kadota, T., Kohda, H. and Miyamoto, J. 1975a. Subchronic toxicity studies of Sumithion, Sumioxon and p-nitrocresol in rats and 92-week feeding study of Sumithion with special reference to change of cholinesterase activity. Bochu Kagaku 40(2): 38-48.

Kadota, T., Okuno, Y. and Miyamoto, J. 1975b. Acute oral toxicity and delayed neurotoxicity of 5 organophosphorus compounds, Salithion, Cyanox, Surecide, Fenitrothion and Fenitrooxon in adult hens. Bochu Kagaku 40(2): 49-53.

Keith, J.O. and Mulla, T.S. 1966. Relative toxicity of five organophosphorus mosquito larvicides to mallard ducks. J. Wildl. Manag. 30: 553-563.

Kimmerle, G. 1962. Toxikologische Untersuchungen mit dem Wirkstoff S5660. Unpublished report from Toxilkolisches und Gewerbehygienisches Laboratorium. As cited in FAO/WHO (1970).

Klimmer, O.R. 1961. Opinion on the toxicity of the compound "S5660" of Farbenfabriken Bayer AG, Leverkusen. Pharmakologisches Institut der Rheinischen Friedrich-Wilhelms-Universitat, Bonn. Report to Farbenfabriken Bayer AG. As cited in FAO/WHO (1970).

Kohli, J.D., Hansan, M.Z. and Gupta, B.N. 1974. Dermal absorption of fenitrothion in rat. Bull. Environ. Contam. Toxicol. 11: 285-290. As cited in NRCC (1975).

Lehotzky, K. and Ungvary, G. 1976. Experimental data on the neurotoxicity of fenitrothion. Acta Pharmacol. Toxicol. 39: 374-382.

Leuck, D.B., Johnson, J.C. Jr., Bowman, M.C., Knox, F.E. and Beroza, M. 1971. Fenitrothion residues in corn silage and their effects on dairy cows. J. Econ. Entomol. 64: 1394-1399. As cited in NRCC (1975).

McCarthy, T.F. 1976. Monitoring health and safety of pesticide workers in forest spraying. In Proceedings of a Symposium on Operational Safety and Environmental Safety. National Research Council of Canada. AFA Technical Report No. 16.

Mitchell, M.F. and Roberts, J.R. 1984. A case study of the use of fenitrothion in New Brunswick. In Effects of pollutants at the ecosystem level. Edited by P.J. Sheehan, D.R. Miller, G.C. Butler and P. Boudreau. SCOPE, John Wiley and Sons Ltd.

Miyamoto, J. 1977. Long-term toxicological effects of fenitrothion in mammals including carcinogenicity and mutagenicity. In NRCC (1977a), pp. 459-496.

Miyamoto, J. and Suzuki, H. 1977. Mutagenicity screening of fenitrothion and its degradation products by Salmonella typhimurium. Sumitomo Chemical Co., Ltd., Japan. As cited in NRCC (1977a).

Miyamoto, J., Sato, Y., Kadota, T. and Fujinami, A. 1963. Studies on the mode of action of organophosphorus compounds. Part II. Inhibition of mammalian cholinesterase in vivo following the administration of Sumithion and Methyl parathion. Agric. Biol. Chem. (Tokyo) 27: 669-76. As cited in FAO/WHO (1970).

Miyamoto, J., Kohda, H. and Kadota, T. 1976. Dominant lethal studies with Sumithion in mice and rats. Sumitomo Chemical Co., Ltd., Japan.

Njagi, G.D.E. and Gopalan, H.N.B. 1981. Mutagenicity testing of herbicides, fungicides and insecticides. I. Chromosome aberrations in Vicia faba. Cytologia 46(1-2): 169-172.

Njagi, G.D.E., Oyolla, F., Hongo-Allego, P. and Gopalan, H.N.B. 1980. Mutagenicity testing of herbicides, fungicides and insecticides. III. Drosophila recessive sex-linked lethals. Bangladesh J. Zool. 8(1): 1-4.

Nishizawa, Y., Fujii, K., Kadota, T., Miyamoto, J. and Sakamoto, H. 1961. Studies on the organophosphorus insecticides. Part VII. Chemical and biological properties of new low toxic organophosphorus insecticide. O,O-Dimethyl-O-(3-methyl-4-nitrophenyl) phosphorothioate. Agric. Biol. Chem. (Jpn) 25: 605-610. As cited in FAO/WHO (1970).

Nosal, M. and Hladka, A. 1968. Determination of the exposure of fenitrothion (O,O-dimethyl-O/3-methyl-4-nitrophenyl/thiophosphate) on the basis of the excretion of p-nitro-m-cresol by the urine of the persons tested. Int. Gewerbepath. Gewerbehyg. 25: 28-38.

NRCC. 1975. Fenitrothion: The effects of its use on environmental quality and its chemistry. Associate Committee on Scientific Criteria for Environmental Quality. National Research Council of Canada. NRCC No. 14104. 162 pp.

NRCC. 1977a. Proceedings of a Symposium on Fenitrothion: The long-term effects on its use in forest ecosystems. Associate Committee on Scientific Criteria for Environmental Quality. National Research Council of Canada. NRCC No. 16073. 628 pp.

NRCC. 1977b. Fenitrothion: The long-term effects of its use in forest ecosystems - Current Status. Associate Committee on Scientific Criteria for Environmental Quality. National Research Council of Canada. NRCC No. 15389. 18 pp.

NRCC. 1982. Aminocarb: The effects of its use on the forest and the human environment. Associate Committee on Scientific Criteria for Environmental Quality. National Research Council of Canada. NRCC No. 18979. 253 pp.

OECD. 1982. Good laboratory practise in the testing of chemicals. Final report of the group of experts on Good Laboratory Practise. Organisation for Economic Co-operation and Development, Paris, France.

Paul, B.S. and Vadlamudi, V.P. 1976. Teratogenic studies of fenitrothion on white leghorn chick embryos. Bull. Environ. Contam. Toxicol. 15(2): 223-229.

Ramakrishna, N. and Ramachandran, B.V. 1978. Malathion A and B esterases of mouse liver - III: In vivo effect of parathion and related PNP-containing insecticides on esterase inhibition and potentiation of malathion toxicity. Biochem. Pharmacol. 27(16): 2049-2054.

Rosival, L., Vargova, M., Szokolayova, J., Cerey, K., Hladka, A., Batora, V., Kovacicova, J. and Truchlik, S. 1976. Contribution to the toxic action of S-methyl fenitrothion. Pest. Biochem. Physiol. 6: 280-286.

Safe, S.H., Plugge, H., Chittim, B. and Crocker, J.F.S. 1977. Analysis of adjuvants used in formulations for the application of organophosphorous pesticides. In NRCC (1977a), pp. 51-76.

Sumitomo Chemical Co., Ltd. 1970. Acute toxicity of Sumithion - Sumitomo Report No. 960-S1478-6-1. Submitted to Swackenhamer, Jan. 7, 1970 - Permission to cite Sumitomo Data Collection. As cited in NRCC (1975).

Sumitomo Chemical Co., Ltd. 1972a. Toxicology studies. Part III. Six-month feeding studies of Sumithion in rats. Japan. As cited in NRCC (1975).

Sumitomo Chemical Co., Ltd. 1972b. Toxicology studies. Part III. Oral toxicity of Sumithion on cattle, sheep and swine. Japan. As cited in NRCC (1975).

Sumitomo Chemical Co., Ltd. 1972c. Toxicology studies. Part I. Acute oral toxicity in rats and mice. Japan. As cited in NRCC (1975).

Sumitomo Chemical Co., Ltd. 1972d. Toxicology studies. Part IV. Delayed neurotoxicity of Sumithion. Japan. Report by Industrial Bio-test Laboratories Inc. IBT No. 8580-09445.

Sumitomo Chemical Co., Ltd. 1972e. Toxicology studies. Part I. Eye and skin irritation in rabbits. Japan. Report by Industrial Bio-test Laboratories Inc. IBT No. 601-04051.

Sumitomo Chemical Co., Ltd. 1973. Toxicolgy studies. Part II. Subacute inhalation toxicity studies of Sumithion on rats and mice. Japan.

Sumitomo Chemical Co., Ltd. 1975a. Two-year dietary administration in the rat. Japan. Report by Hazelton Laboratories Inc. As cited in NRCC (1975).

Sumitomo Chemical Co., Ltd. 1975b. Ninety-two week feeding study of Sumithion in rats with special reference to cholinesterase activity. In Sumithion toxicity data for WHO/FAO Joint Meeting 1974. As cited in NRCC (1975).

Sumitomo Chemical Co., Ltd. 1975c. Ninety-day subacute oral toxicity study, one-year chronic oral cholinesterase activity study and two-year chronic oral toxicity study with technical Sumithion in beagle dogs. Japan. Report by Industrial Bio-test Laboratories Inc. IBT Nos. C9997, C1667, 651-09998.

Sumitomo Chemical Co., Ltd. 1976. Acute oral toxicity and delayed neurotoxicity of Sumithion in hens. Revised Report. Japan. Technical Report No. HT-60-0026.

Sumitomo Chemical Co., Ltd. 1977. Delayed neurotoxicity with Sumithion in hens. Japan. Technical Report No. HT-70-0200.

Sumitomo Chemical Co., Ltd. 1981. Primary eye and skin irritation tests of Sumithion technical in rabbits. Japan. Technical Report No. HT-10-0201.

Sumitomo Chemical Co., Ltd. 1984. Personal communication to the authors.

Suzuki, H. and Miyamoto, J. 1976. Studies on mutgenicity of Sumithion, Cremart and Denmert. Nippon Noyaku Gakkaishi 1(4): 253-260.

Suzuki, H., Miyamoto, J. and Oka, A. 1975. Mutgenicity and radiomimetricity screening of Sumithion. Sumitomo Chemical Co., Ltd., Japan. In Sumithion toxicity data for WHO/FAO Joint Meeting 1974. As cited in NRCC (1975).

Trottier, B., Fraser, A.R., Planet, G. and Ecobichon, D.J. 1980. Subacute toxicity of technical fenitrothion in male rats. Toxicology 17: 29-38.

Ueda, K. and Nishimura, M. 1966. Interim report. Chronic toxicity of Sumithion: Two-year feeding study in rats. Report by Department of Hygiene and Toxicology, Tokyo Dental College to Sumitomo Chemical Co., Ltd., Japan. As cited in FAO/WHO (1970).

Vandekar, M. 1965. Observations on the toxicity of carbaryl, folithion and 3-isopropylphenyl N-methylcarbamate in a village-scale trial in southern Nigeria. Bull World Health Org. 33: 107-115.

WHO. 1958. Procedures for the testing of intentional food additives to establish their safety for use. Tech. Rep. Ser. No. 144. As cited in NRCC (1975).

WHO. 1973. Fenitrothion. In Safe use of pesticides. World Health Organization. Tech. Rep. Ser. No. 513. pp. 18-19. As cited in NRCC (1975).

Wolfe, H.R., Armstrong, J.F., Staiff, D.C. and Comer, S.W. 1972. Exposure of spraymen to pesticides. Arch. Environ. Health 25: 29-31.

PUBLICATIONS

of the
du

Environmental Secretariat
Secrétariat de l'environnement

NRCC Associate Committee on Scientific Criteria for Environmental Quality
CNRC-Comité associé sur les critères scientifiques concernant l'état de l'environnement

NRCC No. / CNRC n°	
12678	Inventory of Pollution-Relevant Research in Canada. Interim Report, Vols. 1, 2. Etat de recherches sur la pollution au Canada. Rapport provisoire, Tomes 1, 2. 1972. 310 pp. $6.50. (Out of print - Edition épuisée)
14108	Inventory of Pollution-Relevant Research in Canada. Vols. 3, 4. Etat de recherches sur la pollution au Canada. Tomes 3, 4. 1975. 558 pp. $6.50.
12226	Environmental Fluoride (Special Report). 1971. 39 pp.
12226	Le fluor dans l'environnement. 1971. 41 pp.
13079	Detection and Inactivation of Enteroviruses in Water. 1973. 26 pp. $1.25.
13080	Problems and Selection of Topics for Compilation of Cause/Effect Data. 1973. 51 pp. $1.25.
13236	Détection et inactivation des entérovirus dans l'eau. 1973. 30 pp. $1.25.
13339	Problèmes et choix de thèmes en vue d'une compilation de données cause/effet. 1974. 45 pp. $1.25.
13501	The Effects of Pulp and Paper Wastes on Aquatic Life with Particular Attention to Fish and Bioassay Procedures for Assessment of Harmful Effects. 1973. 60 pp. $2.50.
13502	L'effet des déchets de pâtes et papier sur la vie aquatique. 1974. 75 pp. $2.50.
13566	A Criteria Digest on Radioactivity in the Environment. 1974. 53 pp. $1.50.
13567	Un résumé de critères sur la radioactivité dans l'environnement. 1974. 45 pp. $1.50.
13682	Lead in the Canadian Environment. 1973. 116 pp. $2.00. (Out of print - See NRCC 16736).
13683	Le plomb dans l'environnement canadien. 1973. 130 pp. $2.00. (Edition épuisée - voir CNRC 16737).
13684	Picloram: The Effects of Its Use as a Herbicide on Environmental Quality. 1974. 128 pp. $5.00.
13685	Piclorame: les effets de son utilisation comme herbicide sur l'état de l'environnement. 1974. 130 pp. $1.00.
13686	A Method of Monitoring Nationally for Possible Delayed Effects of Various Occupational Environments. 1974. 42 pp. $1.25.
13687	Une méthode de surveillance nationale des effets possibles, à long terme, du milieu professionnel sur la santé. 1974. 40 pp. $1.25.
13688	Environmental Cause/Effect Phenomena Relating to Technological Development in the Canadian Arctic. 1974. 125 pp. $2.00.
13689	Phénomènes environnementaux de cause à effet liés au progrès technique dans l'arctique. 1974. 128 pp. $2.00.
13690	The Application of the Phosphorus Loading Concept to Eutrophication Research. 1974. 42 pp. $1.25.
13691	Application du concept de la vitesse d'apport de phosphore par unité de surface à la recherche sur l'eutrophisation. 1974. 44 pp. $1.25.

Available through prepaid purchase orders from

En vente, moyennant commandes prepayées, au Service des

Publications, NRCC/CNRC
Ottawa, Ontario K1A 0R6

NRCC No.
CNRC n°

14094 Chlordane: Its Effects on Canadian Ecosystems and Its Chemistry. 1974. 189 pp. $1.00.

14095 Chlordane: ses effets sur les ecosystèmes canadiens et sa chimie. 1975. 192 pp. $1.00.

14096 Photochemical Air Pollution: Formation, Transport and Effects. 1975. 224 pp. $2.50.

14097 La pollution photochimique de l'air: sa formation, son transport et ses effets. 1976. 203 pp. $2.50.

14098 Endosulfan: Its Effects on Environmental Quality. 1975. 100 pp. $1.25.

14099 Endosulfan: ses effets sur l'état de l'environnement. 1976. 98 pp. $1.25.

14100 Waterborne Dissolved Oxygen Requirements and Criteria With Particular Emphasis on the Canadian Environment. 1975. 111 pp. $2.00.

14101 Exigences et critères relatifs à l'oxygène dissous dans l'eau, et leurs particularités à l'environnement canadien. 1976. 111 pp. $2.00.

14102 Methoxychlor: Its Effects on Environmental Quality. 1975. 164 pp. $2.00.

14103 Méthoxychlore: ses effets sur l'état de l'environnement. 1976. 161 pp. $2.00.

14104 Fenitrothion: The Effects of Its Use on Environmental Quality and Its Chemistry. 1975. 162 pp. $2.00.

14105 Fénitrothion: effets de son utilisation sur l'état de l'environnement, et sa chimie. 1976. 164 pp. $2.00.

14106 Arboviruses and Human Health in Canada. 1975. 35 pp. $1.25.

14107 Arbovirus pathogènes au Canada. 1976. 40 pp. $1.25.

14109 Waste Heat in the Aquatic Environment. 1975. 40 pp. $1.00.

14110 Pollution thermique de l'environnement aquatique. 1976. 68 pp. $1.00.

15015 Sulphur and Its Inorganic Derivatives in the Canadian Environment. 1977. 426 pp. $5.00.

15016 Le soufre et ses dérivés minéraux dans l'environnement canadien. 1978. 441 pp. $5.00.

15017 Effects of Chromium in the Canadian Environment. 1976. 168 pp. $2.00.

15018 Les effets du chrome dans l'environnement canadien. 1977. 162 pp. $2.00.

15019 The Effects of Alkali Halides in the Canadian Environment. 1977. 171 pp. $2.00.

15020 Les effets des halogénures alcalins dans l'environnement canadien. 1977. 171 pp. $2.00.

15021 The Effects of Petroleum Refinery Liquid Wastes on Aquatic Life, with Special Emphasis on the Canadian Environment. 1976. 77 pp. $2.00.

15022 Les effets des déchets liquides du raffinage du pétrole sur la vie aquatique, particulièrement dans l'environnement canadien. 1977. 86 pp. $2.00.

15023 NTA (Nitrilotriacetic Acid) - An Ecological Appraisal. 1976. 46 pp. $1.25.

15024 NTA (acide nitrilotriacétique) - une analyse écologique. 1977. 48 pp. $1.25.

15383 Effects of Noise on Man. 1976. 87 pp. $2.50.

15384 Les effets du bruit sur l'homme. 1977. 92 pp. $2.50.

15385 *Bacillus thuringiensis*: Its Effects on Environmental Quality. 1976. 133 pp. $2.00.

15386 *Bacillus thuringiensis*: ses effets sur l'état de l'environnement. 1977. 127 pp. $2.00.

15387 Medicare Data: Its Use in Defining the Effects of the Environment on Health. 1977. 164 pp. $2.50.

15388 Les statistiques de l'assurance-maladie et leur rôle dans la définition de l'influence de l'environnement sur la santé. 1978. 166 pp. $2.50.

NRCC No.
CNRC n°

15389 Fenitrothion: The Long Term Effects of Its Use in Forest Ecosystems - Current Status. 1977. 18 pp. $1.00.

16074 Fénitrothion: effets à long terme de son utilisation dans les écosystèmes forestiers - situation actuelle. 1977. 20 pp. $1.00.

15391 Effects of Arsenic in the Canadian Environment. 1978. 363 pp. $2.00.

15392 Les effets de l'arsenic sur l'environnement canadien. 1979. 415 pp. $2.00.

16073 Proceedings of a Symposium on Fenitrothion: The Long-Term Effects of Its Use in Forest Ecosystems. Comptes rendus du symposium sur le fénitrothion: les effets à long terme de son utilisation dans les écosystèmes forestiers. 1977. 628 pp. $10.00.

16075 Phenoxy Herbicides: Their Effects on Environmental Quality with Accompanying Scientific Criteria for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD). 1978. 440 pp. $10.00.

16076 Herbicides phénoxy - analyse de leurs effets sur l'état de l'environnement accompagnée de critères scientifiques à l'égard de la 2,3,7,8-tétrachlorodibenzo-p-dioxine (TCDD). 1979. 452 pp. $2.00.

16077 Polychlorinated Biphenyls: Biological Criteria for an Assessment of Their Effects on Environmental Quality. 1978. 172 pp. $2.00.

16078 Polychlorobiphényles: critères biologiques pour évaluer leurs effets sur l'état de l'environnement. 1979. 208 pp. $2.00.

16079 Ecotoxicology of Chlorpyrifos. 1978. 314 pp. $2.00.

16080 Ecotoxicologie du chlorpyrifos. 1979. 250 pp. $2.00.

16081 Environmental Fluoride 1977. 1978. 152 pp. $5.00.

16082 Le fluorure dans l'environnement, 1977. 1979. 175 pp. $2.00.

16446 Effects of Ultraviolet Radiation on Man. 1978. 90 pp. $2.00.

16447 Les effets du rayonnement ultraviolet sur l'homme. 1979. 91 pp. $2.00.

16448 The Biological Effects of Radio-frequency and Microwave Radiation. 1979. 244 pp. $5.00.

16449 Effets biologiques des radiofréquences et des micro-ondes. 1980. 244 pp. $5.00.

16450 The Aqueous Chlorination of Organic Compounds: Chemical Reactivity and Effects on Environmental Quality. 1978. 136 pp. $5.00.

16451 Chloration en milieu aqueux de composés organiques: réactivité chimique et effets sur l'état de l'environnement. 1979. 149 pp. $2.00.

16452 Effects of Asbestos in the Canadian Environment. 1979. 185 pp. $3.00.

16453 Les effets de l'amiante dans l'environnement au Canada. 1980. 202 pp. $3.00.

16454 Copper in the Aquatic Environment: Chemistry, Distribution, and Toxicology. 1979. 227 pp. $3.00.

16455 Le cuivre dans l'environnement aquatique: chimie, répartition et toxicologie. 1980. 249 pp. $3.00.

16736 Effects of Lead in the Environment - 1978. Quantitative Aspects. 1979. 779 pp. $10.00.

16737 Effets du plomb dans l'environnement - 1978. Aspects quantitatifs. 1980. 853 pp. $5.00.

16738 Report of a Special Conference on Hearing Threshold Levels of "Isolated" Human Populations. Comptes rendus du symposium spécial sur les niveaux d'audition des populations humaines "isolées". 1978. 104 pp. $3.00.

16739 Effects of Mercury in the Canadian Environment. 1979. 290 pp. $3.00.

16742 Effets du mercure dans l'environnement au Canada. 1980. 292 pp. $3.00.

NRCC No.
CNRC n°

16740 Carbofuran: Criteria for Interpreting the Effects of Its Use on Environmental Quality. 1979. 191 pp. $2.00.

16741 Carbofurane: critères pour interpréter les effets de son utilisation sur l'état de l'environnement. 1980. 184 pp. $2.00.

16743 Effects of Cadmium in the Canadian Environment. 1979. 148 pp. $5.00.

16744 Les effets du cadmium dans l'environnement canadien. 1979. 150 pp. $3.00.

16745 Effects of Lead in the Canadian Environment - 1978. Executive Report.
Effets du plomb dans l'environnement canadien - 1978. Rapport administratif.
1979. 24 pp. $1.00.

17581 Water Hardness, Human Health, and the Importance of Magnesium. 1979. 119 pp. $3.00.

17582 Dureté de l'eau, santé et importance du magnésium. 1980. 123 pp. $3.00.

17583 Phthalate Esters in the Aquatic Environment. 1980. 108 pp. $3.00.

17584 Esters phtaliques dans l'environnement aquatique. 1981. 110 pp. $3.00.

17585 Executive Reports: Effects of Chromium, Alkali Halides, Arsenic, Asbestos, Mercury, and Cadmium in the Canadian Environment. 80 pp.
Rapports Administratifs: effets du chrome, des halogénures alcalins, de l'arsenic, de l'amiante, du mercure, et du cadmium sur l'environnement canadien. 92 pp.
1980. $3.00.

17586 A Case Study of a Spill of Industrial Chemicals - Polychlorinated Biphenyls and Chlorinated Benzenes. 1980. $5.00.

17587 Effects of Yellow Phosphorus in the Canadian Environment. 1981. 110 pp. $3.00.

17588 Effets du phosphore blanc sur l'environnement canadien. 1981. 112 pp. $3.00.

17589 Zinc in the Aquatic Environment: Chemistry, Distribution, and Toxicology. 1981. 145 pp. $3.00.

17590 Le zinc dans l'environnement aquatique: chimie, répartition et toxicologie. 1981. 152 pp. $3.00.

18128 Intestinal Parasites of Man in the Canadian Environment. 1980. 69 pp. $2.00.

18129 Les parasites intestinaux de l'homme dans l'environnement canadien. 1980. 70 pp. $2.00.

18130 The Ecological Consequences of Dredging and Dredge Spoil Disposal in Canadian Waters. 1982. 142 pp. $5.00.

18131 Les conséquences écologiques du dragage et de l'élimination des résidus du dragage dans les eaux canadiennes. 1983. 150 pp. $5.00.

18132 Effects of Vanadium in the Canadian Environment. 1980. 94 pp. $2.00.

18133 Effets du vanadium dans l'environnement canadien. 1981. 92 pp. $2.00.

18134 Radioactivity in the Canadian Environment. 1980. 129 pp. $3.00.

18135 La radioactivité dans l'environnement canadien. 1981. 133 pp. $3.00.

18156 The Report of the *ad hoc* Panel Convened by the National Research Council of Canada to Review the Spill of Polychlorinated Biphenyls at the Federal Pioneer Ltd. Site in Regina, Saskatchewan. 30 January 1980. 15 pp.

18467 Hydrogen Sulfide in the Atmospheric Environment: Scientific Criteria for Assessing its Effects on Environmental Quality. 1981. 196 pp. $5.00.

18468 Sulfure d'hydrogène dans l'environnement atmospherique: critères scientifiques pour évaluer ses effets sur la qualité de l'environnement. 1982. 204 pp. $5.00.

NRCC No.
CNRC n°

18469 Ethylenethiourea: Criteria for the Assessment of its Effects on Man. 1980. 149 pp. $3.00.

18470 Ethylène-thiourée: critères pour évaluer ses effets sur l'homme. 1981. 187 pp. $3.00.

18471 Pesticide-Pollinator Interactions. 1981. 190 pp. $5.00.

18472 Interactions entre pesticides et pollinisateurs. 1981. 223 pp. $5.00.

18473 Effects of Aerosols on Atmospheric Processes. 1982. 208 pp. $8.00.

18474 Effets des aérosols sur les processus atmosphériques. 1983. 230 pp. $8.00.

18475 Acidification in the Canadian Aquatic Environment: Scientific Criteria for Assessing the Effects of Acidic Deposition on Aquatic Ecosystems. 1981. 369 pp. $10.00.

18476 Acidification dans l'environnement aquatique au Canada: critères scientifiques pour évaluer les effets du dépôt acide sur les écosystèmes aquatiques. 1982. 377 pp. $10.00.

18564 Effects of Inhaled Particles on Human Health: Influence of Particle Size and Shape. 1982. 177 pp. $8.00.

18565 Effets sur la santé des particules absorbées par voie respiratoire: influence de leur taille et de leur forme. 1983. 195 pp. $8.00

18566 Thermal Effects Upon Fishes. 1982. 200 pp. $8.00.

18567 Effets de la pollution thermique sur les poissons. 1983. 210 pp. $8.00.

18568 Effects of Nickel in the Canadian Environment. 1981. 352 pp. $4.00.

18569 Effets du nickel sur l'environnement canadien. 1982. 347 pp. $4.00.

18570 A Screen for the Relative Persistence of Lipophilic Organic Chemicals in Aquatic Ecosystems - An Analysis of the Role of a Simple Computer Model in Screening.
I. A Simple Computer Model as a Screen for Persistence.
II. An Introduction to Process Analyses and Their Use in Preliminary Screens of Chemical Persistence.
1981. 302 pp. $8.00.

18571 Contrôle de la persistance relative de produits organiques lipophiles dans les écosystèmes aquatiques - analyse du rôle d'une simple simulation par ordinateur. 1982. 335 pp. $8.00.

18572 Effects of Propoxur on Environmental Quality with Particular Reference to its Use for Control of Biting Flies. 1982. 238 pp. $8.00.

18573 Les effets du propoxur sur la qualité de l'environnement, notamment quant à son emploi dans la lutte contre les insectes piqueurs. 1982. 253 pp. $8.00.

18574 Polychlorinated Dibenzo-p-Dioxins: Criteria for Their Effects on Man and his Environment. 1981. 251 pp. $8.00.

18575 Polychlorodibenzo-p-dioxines: critères relatifs à leurs effets sur l'homme et son environnement. 1982. 276 pp. $8.00.

18576 Polychlorinated Dibenzo-p-Dioxins: Limitations to the Current Analytical Techniques. 1981. 184 pp. $8.00.

18577 Polychlorodibenzo-p-dioxines: limites des méthodes analytiques actuelles. 1982. 186 pp. $8.00.

18578 Chlorinated Phenols: Criteria for Environmental Quality. 1982. 191 pp. $8.00.

18579 Chlorophénols: critères pour évaluer leurs effets sur l'état de l'environnement. 1982. 217 pp. $8.00.

18976 Farm Animal Manures in the Canadian Environment. 1983. 139 pp. $8.00

18977 L'effet du fumier dans l'environnement canadien. 1983. 145 pp.

18978 Workshop on the Combined Effects of Xenobiotics.
Atelier sur les effets combinés des xenobiotiques.
1982. 253 pp. $8.00.

NRCC No.
CNRC n°

18979 Aminocarb: The Effects of its Use on the Forest and the Human Environment. 1982. 253 pp. $8.00.

18980 Aminocarbe: effets de son utilisation sur la forêt et l'environnement. 1983. 271 pp. $8.00

18981 Polycyclic Aromatic Hydrocarbons in the Aquatic Environment: Formation, Sources, Fate and Effects on Aquatic Biota. 1983. 209 pp. $8.00

18983 The Need for New Directions in Toxicological Funding.
Le besoin d'une nouvelle politique en ce qui concerne les subventions dans le domaine toxicologique. 1982. 11 pp. $2.00.

19244 Ultrasound: Characteristics and Biological Action. 1981. 284 pp. $8.00.

19245 Les ultrasons: caractéristiques et action biologique. 1982. 284 pp. $8.00.

19246 The Effects of Cyanides on Aquatic Organisms with Emphasis upon Freshwater Fishes. 1982. 139 pp. $5.00.

19247 Effets des cyanures sur les organismes aquatiques, notamment sur les poissons d'eau douce. 1983. 144 pp. $5.00.

19248 Biting Flies in Canada: Health Effects and Economic Consequences. 1982. 157 pp. $5.00.

19249 Insectes piqueurs au Canada: effets sur la santé et conséquences économiques. 1983. 169 pp. $5.00.

19250 Radioactivity in the Canadian Aquatic Environment. 1983. 292 pp. $8.00

19251 La radioactivité dans l'environnement aquatique au Canada. 1983. 292 pp. $8.00

19252 Data Sheets on Selected Toxic Elements. 1982. 61 pp. $5.00.

19253 Fiches de données sur certains éléments toxiques. 1983. 48 pp. $5.00

20640 Cold: Special Aspects in the Canadian North. 1983. 33 pp. $3.00.

20641 Aspects particuliers du froid dans le nord canadien. 1983. 33 pp. $3.00

20642 Proceedings of a Symposium on Monitoring and Assessment of Airborne Pollutants with Special Emphasis on Long-range Transport and Deposition of Acidic Materials Workshop on Air and Precipitation Monitoring Networks.
Comptes rendus du symposium sur la surveillance et l'évaluation des polluants en suspension dans l'air et notamment sur le transport à grande distance et le dépôt de substances acides Atelier sur les réseaux de surveillance de l'air et des précipitations.
1983. 502 pp. $8.00.

20643 Interactions of Selenium. 1983. 85 pp. $5.00

20644 Interactions du sélénium avec d'autres éléments. 1983. 85 pp. $5.00

20645 Impact Assessments in Lotic Environments - Methoxychlor. 1983. 130 pp. $5.00

20646 Evaluation des effets du méthoxychlore dans les milieux lotiques. 1984. 144 pp. $5.00

20647 2,4-D: Some Current Issues. 1983. 99 pp. $5.00

20648 2,4-D: quelques questions actuelles. 1984. 106 pp. $5.00

22492 Post "IBT" Assessment of Critical Laboratory Studies on the Mammalian and Avian Toxicology of Fenitrothion. 1984. 110 pp. $5.00

Available through prepaid purchase orders from

En vente, moyennant commandes prepayées, au Service des

Publications, NRCC/CNRC
Ottawa, Ontario K1A 0R6

ORGANIZATION CHART

ASSOCIATE COMMITTEE ON SCIENTIFIC CRITERIA FOR ENVIRONMENTAL QUALITY